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TESTS OF PITUITARY-ADRENAL SUPPRESSIBILITY IN THE DIAGNOSIS OF CUSHING'S SYNDROME*

GRANT W. LIDDLE, M.D.
Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

ABSTRACT

Past attempts to test suppressibility of pituitary-adrenal function by the use of exogenous corticoids have yielded inconsistent findings in patients with Cushing's syndrome. The present study indicates that, with proper selection of suppressive agent and adjustment of dosage, valuable diagnostic information can be obtained from such tests. Δ^1-9α-Fluorocortisol (ΔFF) and its 16α-methylated analog (dexamethasone) were employed as suppressive agents. At dosage levels of 0.5 mg. every six hours for 8 doses these agents induced almost complete suppression of 17-hydroxycorticoid excretion in all 54 endocrinologically normal subjects tested. In contrast, all 35 of the patients with true Cushing's syndrome who were studied maintained relatively high urinary 17-hydroxycorticoid levels during such treatment. At these low dosages, therefore, the suppressive agents were useful in separating patients with Cushing's syndrome from those with normal adrenal function. Administration of ΔFF or dexamethasone in larger dosages of 2.0 mg. every six hours for 8 doses was used to separate patients with ACTH-dependent hyperadrenocorticism from those with autonomously functioning adrenal tissue. In response to large doses of suppressive agents, all patients with bilateral adrenocortical hypersecretion exhibited a definite decrease in 17-hydroxycorticoid excretion, whereas patients with adrenocortical tumors did not. The results support the view that the primary disorder in Cushing's syndrome with bilateral adrenocortical hypersecretion involves alteration of pituitary function in such a way that ACTH secretion is not suppressed by normal levels of cortisol.

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INTRODUCTION

Evolution of concepts of Cushing's syndrome. In his description of the syndrome which was to bear his name, Cushing (1) suggested that the metabolic aberrations which were characteristic of the disorder were secondary to an increase in basophilic cells of the pituitary. Soon thereafter it was recognized that patients with adrenocortical tumors without pituitary basophilism frequently exhibited the clinical and metabolic abnormalities of Cushing's syndrome. Because the pituitary was known to secrete a hormone (adrenocorticotropin, ACTH) capable of stimulating adrenocortical activity it was postulated that the common final pathway in the pathogenesis of Cushing's syndrome was hypersecretion of adrenocortical hormones (2). Albright (3) suggested that the characteristic features of Cushing's syndrome were best explained as the effects of excessive secretion of carbohydrate-regulating or "S hormone" by the adrenal cortex. Through the studies of Nelson *et al.* (4) and Romanoff *et al.* (5) it ultimately became apparent that the only "S hormone" secreted by the human adrenal in quantities large enough to be of much physiologic consequence was cortisol (hydrocortisone). As methods for assaying cortisol and its metabolic derivatives in biologic fluids became available, it was recognized that a cardinal feature of Cushing's syndrome was an abnormally high level of so-called "17-hydroxycorticoids" in blood and urine (6–10). Cushing's syndrome could now be defined as a group of clinical and metabolic abnormalities resulting from a chronic excess of cortisol.

Normal and abnormal regulation of cortisol secretion. Under normal circumstances the adrenocortical secretion of cortisol is governed by the amount of ACTH secreted by the adenohypophysis. Since one of the characteristic actions of cortisol is suppression of ACTH secretion, the ACTH-cortisol relationship can be depicted as a servomechanism in which cortisol levels tend to be self-regulating; an increase in cortisol initiates a sequence of events which ultimately restrains further secretion of cortisol.

The fact that in Cushing's syndrome cortisol secretion is manifestly excessive implies that the normal restraint on pituitary or adrenal function is not operating properly. Two possibilities are apparent. Either the ACTH-secreting mechanism is not restrained by normal levels of cortisol, or adrenal tissue is no longer dependent upon the stimulatory influence of ACTH and secretes excessive amounts of cortisol autonomously. In the latter situation it may be assumed that the excessive amounts of cortisol coming from the autonomous adrenal tissue suppress the ACTH-secreting mechanism.

Against the background of these theoretical considerations the present study was designed in an effort to develop a standard ACTH-suppression

test and to assess the merits of such a test in the diagnosis of Cushing's syndrome.

METHODS

Test conditions and laboratory procedures. The subjects were 180 hospitalized patients and ambulatory hospital employees. Complete 24-hour urine collections were made daily throughout the test period. Specimens were preserved with a 5 per cent solution of thymol in glacial acetic acid; 5 ml. of this solution was added to the specimen bottle at the beginning of each 24-hour collection period. At least two 24-hour collections were obtained as control specimens at the beginning of each study. Then Δ^1-9α-fluorocortisol (ΔFF) was administered orally in dosage of 0.5 mg. every six hours during at least two additional days of urine collection. In several studies, standard intravenous ACTH tests were interposed between the control period and the ΔFF test period. Depot ACTH was never employed because of the possibility that its effect might carry over into the ΔFF period. In several of the more recent studies, dexamethasone, the 16α-methyl analogue of ΔFF, was used in dosage of 0.5 mg. every six hours in place of ΔFF. Whenever corticosteroid levels failed to fall in response to ΔFF or dexamethasone in a dosage of 0.5 mg. every six hours, the test was repeated employing 2.0 mg. every six hours.

In all studies, urinary 17-hydroxycorticoids were determined by a modification of the method of Silber and Porter (11), urinary 17-ketosteroids were assayed by a modification of the method of Callow, Callow and Emmens (12), and urinary creatinine (as a check on the completeness of urine collection) was measured by the method of Folin as modified by Hawk, Oser and Summerson (13). In several studies, serial determinations of plasma 17-hydroxycorticoid concentration were made by a modification of the method of Silber and Porter.

Selection and classification of subjects. "Normal" subjects were 54 hospital employees and patients in whom the medical history and physical examination provided no basis for suspecting any endocrinologic disorder; acutely ill or postoperative patients were not included. All of the 114 cases referred to the author during a three-year period, in which the referring physician suspected Cushing's syndrome were included in this study. Observations were also made on 12 patients with pituitary tumor but no clinical signs of Cushing's syndrome.

A diagnosis of Cushing's syndrome was considered established in the 35 cases satisfying all of the following three criteria: 1) definite clinical features of Cushing's syndrome, 2) consistent elevation of basal urinary 17-hydroxycorticoid excretion, and 3) morphologic evidence of pituitary or adrenal enlargement and/or a favorable response to adrenalectomy or pituitary irradiation.

RESULTS AND COMMENTS

Development of a standard ACTH-suppression test

It was considered desirable that the steroid selected for the purpose of suppressing ACTH be one which did not itself contribute appreciably to the level of 17-hydroxycorticoids in the urine. At the time this study was initiated in 1955 the most suitable agent for this purpose was Δ^1-9α-fluorocortisol (ΔFF). In a dosage as low as 0.5 mg. every six hours ΔFF was capable of suppressing ACTH, thereby reducing the levels of plasma and urinary 17-hydroxycorticoids to negligible values (14). Recently the 16α-

methyl analogue of ΔFF—dexamethasone (Fig. 1)—has been found equally suitable as an ACTH suppressive agent. Dexamethasone has the dual advantage over ΔFF of being relatively free of sodium-retaining and potassium-wasting side-effects and of being generally available to physicians.

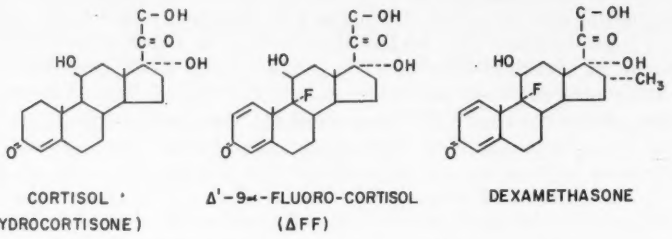

FIG. 1. Structural formulas of cortisol, Δ^1-9α-fluorocortisol and dexamethasone.

Dose-response curves

Dose-response curves characterizing the suppressive action of ΔFF and dexamethasone are depicted in Figure 2. At weekly intervals on a randomized schedule, each of 6 normal subjects was treated for two days with a particular dose of the suppressive agent.[1] With either agent, maximal suppression was consistently observed at the dosage level of 0.5 mg. every six hours. This dosage was selected as the standard in testing a larger group of normal subjects.

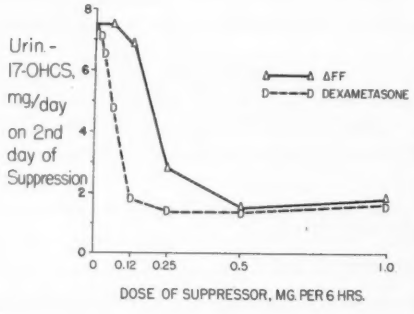

FIG. 2. Dose-response curves depicting the suppressive effect of ΔFF and dexamethasone on urinary 17-hydroxycorticoid excretion. Each curve represents the average of values obtained in the same 6 normal subjects. The suppressive agent was administered orally every six hours for two days. Tests were performed at weekly intervals in order to permit complete recovery between treatments; completeness of recovery was confirmed by determining urinary 17-hydroxycorticoids for two days immediately preceding each test.

[1] Throughout the remainder of this report "ΔFF" will often be used as a generic term, applying to both Δ^1-9α-fluorocortisol and dexamethasone. Although these two compounds were used interchangeably in the present study, it is possible that smaller doses of dexamethasone would be appropriate, in view of the apparent greater potency of this agent. The question is currently under study.

Results of standard ACTH-suppression test in normal subjects

Under basal conditions, normal adults were found to excrete not less than 3 mg. nor more than 12 mg. of 17-hydroxycorticoids per day. In response to ΔFF (0.5 mg. every six hours), all 54 of the normal subjects tested exhibited a decrease in the urinary excretion of 17-hydroxycorticoids to less than 2.5 mg. on the second day of the test (Fig. 3).

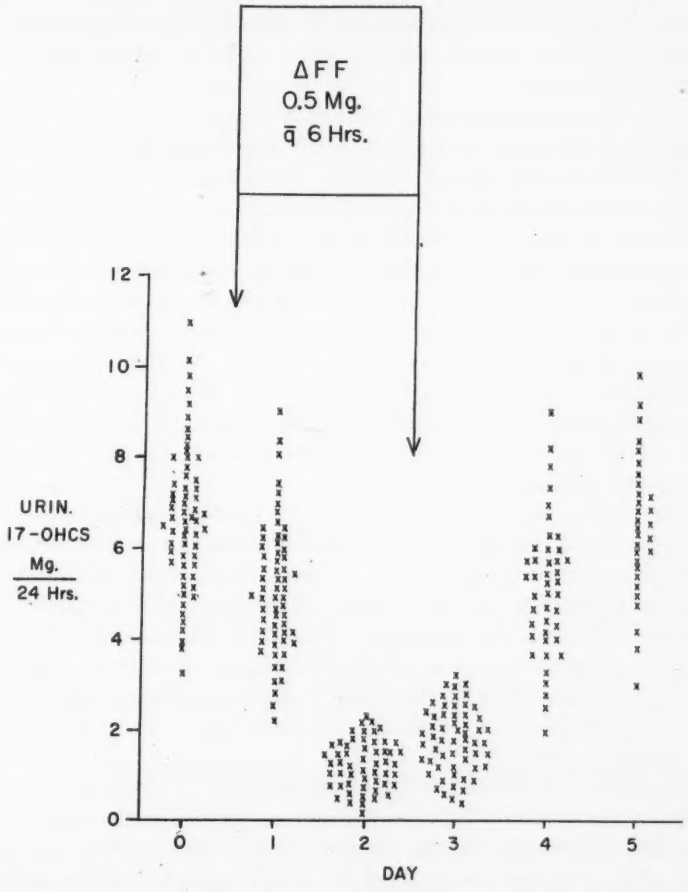

FIG. 3. Urinary 17-hydroxycorticoid levels in 54 normal subjects, as influenced by ΔFF or dexamethasone in a dosage of 0.5 mg. every six hours. Some subjects were studied more than once. Several were not followed during the post-treatment recovery phase.

Results of standard ACTH-suppression test in patients suspected of having Cushing's syndrome

The test was performed in 114 patients suspected of having Cushing's syndrome. In 65 of these "suspects" the diagnosis of Cushing's syndrome was abandoned when the basal levels of urinary 17-hydroxycorticoid excretion were found to be consistently normal. Of the 49 patients who had elevated basal levels of urinary 17-hydroxycorticoids, a final diagnosis of Cushing's syndrome due to bilateral adrenocortical hypersecretion was made in 27 cases, and a final diagnosis of Cushing's syndrome due to adrenocortical tumor was made in 8 cases. No final diagnosis was made in 14 cases. Each of these groups will be given detailed consideration in the following paragraphs.

Patients with normal basal urinary levels of 17-hydroxycorticoids (Table 1). Although the diagnosis of Cushing's syndrome is untenable in the absence of certain well-known clinical features, these clinical characteristics are not limited to patients with hyperadrenocorticism. In the present study patients with clinical features mimicking those of hyperadrenocorticism but with normal basal 17-hydroxycorticoid levels were not considered to have true Cushing's syndrome. None of the 65 patients in this group exhibited such convincing clinical pictures as to raise serious doubt as to the validity of this diagnostic criterion. In all 65, urinary 17-hydroxycorticoid excretion fell to less than 4 mg. per twenty-four hours in response to administration of 0.5 mg. of ΔFF every six hours. The ACTH suppression test, therefore, was considered to be of confirmatory value in excluding the diagnosis of Cushing's syndrome.

Patients with Cushing's syndrome due to bilateral adrenocortical hypersecretion (Table 2). In approximately half of these 27 patients the diagnosis of Cushing's syndrome was obvious before 17-hydroxycorticoid determinations were performed. In all 27 cases, basal urinary 17-hydroxycorticoid levels were elevated. The diagnosis of bilateral adrenocortical hyperfunction (as opposed to autonomous adrenocortical tumor) was confirmed in every case by anatomic findings at the time of adrenal exploration, by the favorable response to irradiation of the pituitary, or by x-ray evidence of a pituitary tumor.

All 27 patients exhibited definite resistance to the suppressive influence of ΔFF. In no instance did the 24-hour urinary 17-hydroxycorticoid excretion fall to less than 4 mg. on the second day of treatment with 0.5 mg. of ΔFF every six hours (Fig. 4). In 16 cases there was little or no change in urinary 17-hydroxycorticoids in response to this dosage of ΔFF. In order to determine whether the resistance of these 16 patients to suppression was absolute or merely a matter of degree, they were given 2.0

TABLE 1. DATA ON 65 PATIENTS SUSPECTED OF HAVING CUSHING'S SYNDROME BUT IN WHOM URINARY STEROID [illegible] NORMAL

Patient	Sex & Age	Obesity	Glucose tolerance	Blood pressure (mm.Hg)	Osteoporosis	Ecchymoses	Striae	Edema	Serum K+ (mEq./L.)	Emotional instability	Oligoamenorrhea	Hirsutism	Weakness	Urinary 17-ketosteroids (mg./24 hrs.)	Urinary 17-hydroxycorticoids (mg./24 hrs.)			
															Basal	1st day of ACTH, 50 units i.v., 8 hrs.	2nd day of ΔFF, 0.5 mg. q. 6 hrs.	2nd day of ΔFF, 2.0 mg. q. 6 hrs.
J.A.	F 18	General	Impaired	120/80	—	No	Yes	No	—	No	Yes	No	No	12	10	25	1	
N.A.	F 31	General	Impaired	130/85	—	No	No	No	—	No	No	No	No	19	10	45	1	
H.A.	F 43	General	Normal FBS*	210/120	No	No	No	No	4.6	Yes	No	Moderate	No	12	8	30	2	
L.B.	F 58	Central	Diabetes	210/110	Slight	No	No	No	5.0	Yes	—	No	No	2	8	—	1	
E.Bo.	F 28	No	Normal FBS	138/84	No	No	No	Yes	4.4	Yes	No	Slight	Yes	11	9	—	2	
E.Bra.	F 43	Central	Diabetes	114/76	—	No	No	No	—	Yes	No	Moderate	No	12	8	—	2	
A.Bre.	F 39	General	Diabetes	190/90	No	No	No	Yes	4.2	No	No	Slight	No	9	11	38	2	
A.Bu.	F 35	General	Impaired	210/130	Slight	No	No	No	4.2	No	No	Slight	No	14	6	21	2	
J.B.	M 8	Massive	—	140/100	No	No	Yes	No	—	No	—	No	No	4	7	—	1	
S.C.	F 34	General	—	130/80	—	No	No	No	4.9	No	Yes	Moderate	No	11	7	—	2	
C.C.	F 5	General	Normal FBS	95/60	No	No	No	No	—	No	—	Slight	No	2	4	—	1	
M.C.	F 28	Massive	Impaired	180/110	No	No	No	Yes	4.3	No	Yes	Moderate	No	5	5	19	1	
M.D.	F 29	General	Normal FBS	130/80	—	No	No	No	—	No	Yes	Slight	No	7	8	36	2	
V.D.	F 25	No	Impaired	110/60	No	No	No	No	—	No	No	Slight	No	7	5	33	2	
R.D.	F 47	Central	Diabetes	160/80	No	No	No	No	4.7	No	No	Moderate	No	6	10	—	1	
V.D.	F 29	General	Normal FBS	144/100	—	No	No	No	—	Yes	Yes	Slight	No	12	8	29	1	
H.D.	F 57	Massive	Impaired	160/90	Moderate	No	No	Yes	4.8	No	—	Moderate	No	7	10	74	3	
N.D.	F 15	General	Diabetes	140/92	Slight	No	Yes	No	4.4	No	Yes	No	No	2	8	31	2	
M.F.	F 40	General	Diabetes	130/80	No	No	No	No	4.9	Yes	No	Moderate	No	10	9	45	2	
J.F.	F 12	General	Normal	140/90	No	Yes	Yes	No	4.8	No	No	No	No	6	10	—	3	
D.F.	F 30	Central	Normal	122/80	No	No	No	Yes	4.4	No	Yes	Slight	No	16	9	—	2	
B.F.	F 24	General	—	150/90	No	No	No	No	—	No	Yes	Slight	No	8	9	—	3	
H.G.	F 13	General	Normal FBS	120/80	—	No	No	No	—	No	No	No	No	4	8	—	2	
R.H.	F 57	Central	Diabetes	180/110	No	No	Yes	Yes	4.1	No	—	Moderate	No	3	6	18	1	
N.J.	F 35	General	Impaired	115/75	—	No	No	Yes	4.3	Yes	No	No	Yes	13	9	37	2	
R.J.	M 11	General	Normal FBS	110/85	No	No	No	No	4.2	Yes	—	Precocious puberty	No	8	7	40	1	
V.J.	F 23	No	Normal FBS	110/70	No	No	No	No	4.4	No	Yes	Slight	Yes	12	8	—	2	
B.J.	F 25	General	Normal	120/70	No	No	No	No	4.7	No	No	Moderate	No	13	6	34	2	
M.L.	F 53	Central	Impaired	170/95	No	No	No	No	—	Yes	No	Slight	No	6	8	30	1	
B.La.	F 25	General	—	110/70	No	No	No	No	—	No	Yes	Slight	No	8	5	24	1	
B.Led.	F 37	General	Normal FBS	124/86	No	No	No	No	4.5	Yes	Yes	Moderate	No	6	7	—	1	
C.L.	M 42	General	Normal FBS	190/110	No	No	Yes	Yes	4.4	No	—	—	No	10	11	—	4	
B.Lew.	F 20	General	Normal FBS	118/75	No	No	No	No	4.4	Yes	No	Moderate	No	13	10	—	1	
A.L.	F 36	General	Diabetes	150/100	No	No	No	No	—	Yes	No	Moderate	No	7	11	31	2	
I.M.	F 21	Central	Normal FBS	110/70	—	No	No	No	4.9	No	No	Slight	No	14	8	—	1	
E.M.	F 25	No	Normal	125/75	No	No	No	No	4.3	Yes	Yes	Marked	No	23	8	28	2	
L.M.	F 37	Central & general	Diabetes	170/112	No	No	No	No	4.1	No	No	Moderate	Yes	20	9	33	1	
S.M.	F 36	No	Normal FBS	120/78	—	No	No	No	4.6	No	No	Slight	No	12	6	—	1	
N.M.	F 12	General	—	115/70	—	No	No	No	4.1	No	No	No	No	9	8	—	1	
G.M.	F 48	Central & general	Diabetes	120/80	—	No	No	Yes	4.0	Yes	No	No	No	5	7	37	1	
R.N.	F 23	General	Impaired	170/110	No	No	No	No	4.7	No	Yes	Marked	No	11	9	43	1	1
B.O.	M 62	Central	Normal	230/150	No	No	No	No	4.3	No	—	—	No	4	8	—	3	
B.P.	F 17	General	Normal	130/90	No	No	No	No	4.6	No	No	Moderate	No	16	9	38	1	
F.P.	F 35	General	Normal	130/70	No	No	No	No	—	Yes	No	Slight	No	7	8	44	3	
E.R.	F 23	General	Normal FBS	120/76	No	No	Yes	No	4.9	Yes	Yes	No	No	6	7	31	1	
J.R.	M 44	General	Normal FBS	158/100	Slight	No	No	No	4.9	Yes	—	—	No	18	11	44	3	
L.R.	M 39	General	Diabetes	150/85	No	No	No	No	3.9	Yes	—	—	No	—	9	—	2	2
C.R.	M 15	General	Impaired	130/100	No	No	No	No	4.5	No	—	—	No	10	9	—	2	
G.R.	F 44	General	No	140/80	Slight	No	No	No	—	No	No	Moderate	No	9	8	—	1	
M.Sa.	F 35	General	Normal FBS	130/75	No	No	No	No	—	Yes	No	No	No	7	5	30	1	
M.Sc.	F 47	General	Impaired	136/86	—	No	No	No	4.7	No	No	No	No	9	7	39	2	
F.S.	F 35	General	Impaired	130/88	—	No	No	No	—	Yes	No	Slight	No	10	9	26	2	
M.Sh.	F 37	General	Impaired	130/70	No	No	No	No	4.5	Yes	No	Slight	Yes	12	10	39	3	
G.S.	F 25	Central	Diabetes	140/96	No	No	No	No	4.7	No	Yes	Moderate	No	17	8	27	1	
C.S.	M 61	General	Impaired	220/130	Moderate	No	No	Yes	4.4	No	—	—	No	7	4	15	2	
J.S.	F 46	General	Normal FBS	170/85	No	Yes	No	No	4.5	No	No	Slight	No	7	9	—	2	
B.S.	F 24	General	Impaired	130/80	Slight	No	No	No	4.7	Yes	Yes	No	No	9	9	40	2	
N.T.	F 21	Central & general	Normal	120/80	No	No	No	No	—	No	No	Slight	No	6	12	45	2	
M.T.	F 48	Massive	Diabetes	180/100	Slight	No	No	No	4.4	No	No	Slight	No	7	8	25	3	
R.T.	F 23	No	—	130/80	—	No	No	No	—	No	Yes	No	No	12	9	23	1	
I.W.	F 36	Central	Normal FBS	160/95	No	Yes	No	Yes	5.1	Yes	No	Slight	Yes	4	5	—	2	
M.W.	F 24	General	Normal	140/62	No	No	No	No	—	No	Yes	Slight	No	20	7	25	1	
O.W.	F 36	No	Normal FBS	110/70	—	No	No	No	4.2	Yes	Yes	Slight	No	15	6	33	1	
P.W.	F 21	No	Normal FBS	120/70	No	No	No	No	4.2	No	Yes	Marked	No	17	11	68	3	
K.W.	F 21	General	Normal FBS	110/70	—	No	No	No	4.0	No	Yes	Slight	No	24	7	23	1	

* Fasting blood sugar level.

TABLE 2. DATA ON 27 PATIENTS WITH CUSHING'S SYNDROME

Patient	Sex & Age	Obesity	Glucose tolerance	Blood pressure (mm.Hg)	Osteoporosis	Ecchymoses	Striae	Edema	Serum K^+ (mEq./L.)	Emotional instability	Oligo-amenorrhea
H.B.	M 15	Central	Impaired	138/88	Marked	No	No	No	4.2	No	—
R.B.	M 49	Central	Impaired	190/100	Severe	Yes	Yes	Yes	3.1	No	—
B.B.	F 35	Central	Impaired	150/90	Moderate	Yes	No	No	4.9	Yes	Yes
V.C.	F 35	Central	Mild diabetes	170/100	Marked	Yes	Yes	Yes	4.7	Yes	Yes
T.D.	M 7	Central	Impaired	135/85	Slight	No	No	No	4.7	No	—
P.D.	F 14	Central	Impaired	130/85	Marked	Yes	Yes	No	4.8	No	Yes
V.E.	F 55	Slight	Impaired	210/120	Slight	No	No	No	4.1	No	—
F.E.	M 25	Central	Impaired	120/90	Marked	Yes	No	No	4.5	No	—
A.H.	M 43	Central	Diabetes	150/80	Slight	Yes	No	Yes	3.6	Psychotic	—
P.H.*	M 21	Central	Normal	140/110	No	Yes	Yes	Yes	4.6	No	—
M.J.	F 30	Central	Mild diabetes	180/115	Yes	No	No	No	4.9	No	Yes
R.J.	F 32	Central	Impaired	140/90	No	No	No	No	4.3	Yes	Yes
R.K.†	F 37	Central	Impaired	160/110	Marked	No	No	No	4.1	Yes	Yes
C.L.	M 41	Central	Impaired	160/100	Marked	No	No	Yes	4.3	Yes	—
B.M.	F 26	Central	Impaired	130/80	Minimal	Yes	No	No	4.4	No	Yes
I.M.‡	F 30	Central	—	140/100	Yes	No	No	No	Normal	No	Yes
T.N.	M 15	Central	Impaired	168/118	Slight	Yes	Yes	No	4.5	No	—
J.N.§	M 25	Central	Impaired	135/100	—	No	Yes	Yes	4.9	No	—
A.O.	F 16	Central & general	Impaired	144/96	No	No	No	No	4.1	No	Yes
M.P.	F 55	Central	Impaired	235/125	—	Yes	No	Yes	4.9	Yes	—
V.P.	F 37	Central	Diabetes	220/120	—	No	No	No	4.2	No	No
M.R.¶	F 11	Central	Impaired	125/70	Yes	No	Yes	No	4.2	Yes	No
M.Si.	F 15	Central & general	Impaired	135/90	No	No	No	No	4.0	Psychotic	No
P.S.	F 27	Central	Impaired	130/90	Moderate	No	Yes	No	4.4	Yes	Yes
M.Su.	F 38	Central	Impaired	140/90	—	No	No	No	4.5	No	Yes
E.W.	F 33	Slight central	Normal	124/86	Marked	Yes	No	Yes	4.6	Yes	No
C.W.	M 35	Central	—	190/105	Moderate	Yes	No	Yes	4.4	No	—

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mg. of ΔFF every six hours, for two or three days. In all 16 cases a decrease in 17-hydroxycorticoids to less than 50 per cent of basal values was observed on the second or third day of ΔFF administration.

It is apparent that even though these patients differed from *normal* subjects in resisting the suppressive influence of small doses of ΔFF, their pituitary-adrenal systems were not absolutely autonomous but could be suppressed when sufficiently large amounts of ΔFF were employed.

DUE TO BILATERAL ADRENOCORTICAL HYPERSECRETION

Hirsutism	Weakness	Urinary 17-ketosteroids (mg./24 hrs.)	Urinary 17-hydroxycorticoids (mg./24 hrs.)				Comments
			Basal	1st day of ACTH, 50 units i.v., 8 hrs.	2nd day of ΔFF, 0.5 mg. q. 6 hrs.	2nd day of ΔFF, 2.0 mg. q. 6 hrs.	
—	Yes	29	23	69	16	3	Excellent response to bilat. adrenalectomy. Glands morphologically normal.
—	Yes	16	10	20	8	2	No 17-OH-CS studies until 1 yr. after successful treatment with pituitary irrad. and removal of one hyperplastic adrenal. Pre-irrad. 17-KS, 43 mg./24 hrs.
Slight	Yes	16	14	35	8	4	Pituitary tumor by x-ray. Hyperpigmentation of recent onset.
Slight	Yes	13	23	42	16	5	Previous unilat. adrenalectomy unsuccessful. Good response to removal of second gland. Gross and microscopic adrenal hyperplasia.
Downy	Yes	4	12	32	7	2	Excellent response to pituitary irrad.
Downy	No	7	14	31	10	4	Good response to bilat. adrenalectomy; glands morphologically normal.
Slight	No	12	17	52	5	3	Enlarged sella turcica and features of acromegaly.
—	Yes	20	19	49	16	7	Previous unilat. adrenalectomy unsuccessful. Good response to removal of second gland. Adrenal weights 11 Gm. and 14 Gm.
—	Yes	15	17	73	17	5	Marked improvement following bilateral adrenalectomy. Adrenals weighed 19 Gm. and 13 Gm.
—	No	61	30	76	29	—	Operative findings: bilat. adrenocort. hyperplasia. Excellent response to bilat. adrenalectomy.
Moderate	No	20	18	60	23	6	Good response to bilat. adrenalectomy.
Extreme	No	35	28	65	21	7	Good response to hypophysectomy.
Slight	Yes	25	17	59	16	8	Operative findings: slight adrenal hyperplasia. Excellent remission following pituitary irrad.
—	Yes	11	16	52	15	5	Operative findings: adrenal glands morphologically normal.
Slight	Yes	24	17	61	7	2	Basal steroid excretion became normal after pituitary irrad.
—	Yes	24	16	51	11	6	Operative findings: adrenocort. hyperplasia.
—	Yes	22	19	72	19	4	Excellent response to pituitary irrad.
—	Yes	9	36	77	35	21	17-OH-CS, 14 mg. on 3rd day of dexamethasone (2 mg. q. 6 hrs.). Adrenal glands morphologically normal. Chromophobe adenoma of pituitary.
No	No	12	16	52	8	1	Basal steroid excretion became normal after pituitary irrad.
Slight	Yes	15	21	65	18	10	Death; postop. hemorrhage. Adrenal glands morphologically normal.
Slight	No	14	12	32	15	5	Good response to bilat. adrenalectomy. Glands morphologically normal.
Downy	No	4	12	24	5	—	Failed to respond to unilat. adrenalectomy. Good response to removal of second gland. Adrenals hyperplastic.
Downy	No	12	16	59	8	5	Basal steroid excretion became normal after pituitary irrad.
Downy	Yes	14	21	56	18	3	Good response to bilat. adrenalectomy. Glands morphologically normal
Marked	No	12	15	62	4	—	Enlarged sella turcica.
No	No	16	17	77	8	5	Removal of left adrenal (showing adenoma and hyperplasia) failed to lower steroid excretion levels. Later there was an excellent response to pituitary irrad.
—	Yes	23	17	45	13	4	Good response to bilat. adrenalectomy. Glands slightly hyperplastic.

Patients with Cushing's syndrome due to adrenocortical tumor (Table 3). The diagnosis of adrenocortical tumor was made preoperatively and confirmed at the time of adrenal exploration in 8 of the cases in this group. Whenever it could be identified, the nontumorous adrenocortical tissue was atrophic. Whenever it was possible to remove the tumor entirely, adrenocortical hypofunction was demonstrable in the postoperative period, indicating that only the tumor had been hyperactive.

The diagnosis of Cushing's syndrome was obvious in most of these patients even before 17-hydroxycorticoid determinations were performed. In all 8 cases, basal urinary 17-hydroxycorticoid excretion was elevated,

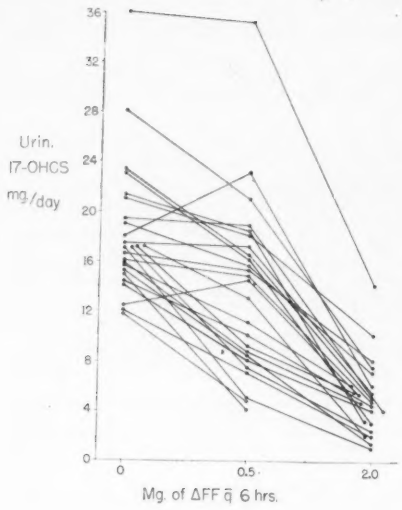

FIG. 4. Urinary 17-hydroxycorticoid excretion in patients with Cushing's syndrome due to bilateral adrenocortical hypersecretion. Left: average basal levels. Middle: values observed during attempted suppression with ΔFF or dexamethasone in a dosage of 0.5 mg. every six hours. Right: values observed during suppression with ΔFF or dexamethasone in a dosage of 2.0 mg. every six hours.

but in only 2 were the basal values above the range seen in cases of bilateral adrenocortical hypersecretion. Like patients with bilateral adrenocortical hypersecretion, those with adrenal tumors and Cushing's syndrome resisted the suppressive influence of small dosages of ΔFF (0.5 mg. every six hours). In addition, however, patients with adrenal tumors completely resisted the suppressive influence of large dosages of ΔFF (2.0 mg. every six hours) (Fig. 5). It was thus possible to distinguish "tumorous" from "nontumorous" Cushing's syndrome with a high degree of reliability.

Patients with equivocal evidence of Cushing's syndrome. In Table 4 are

TABLE 3. DATA ON 8 PATIENTS WITH CUSHING'S

Patient	Sex & Age	Obesity	Glucose tolerance	Blood pressure (mm.Hg)	Osteoporosis	Ecchymoses	Striae	Edema	Serum K^+ (mEq./L.)	Emotional instability	Oligoamenorrhea
I.B.*	F 38	Central	—	210/130	No	No	No	No	4.5	No	No
A.D.	F 49	Central	Impaired	190/110	Yes	No	No	No	4.3	Yes	Yes
L.J.	M 48	Central	Impaired	200/120	Marked	Yes	Yes	Yes	3.2	Psychotic	—
G.K.	F 45	Central	Impaired	200/110	Severe	Severe	Yes	Yes	2.9	Yes	Yes
P.†	F 24	Central	Normal	140/114	Yes	Yes	Yes	No	4.0	No	Yes
M.S.	F 39	Central	Impaired	150/90	Yes	Yes	No	No	4.1	Yes	No
V.W.	F 57	Central	Impaired	230/120	Yes	Yes	No	Yes	2.5	Yes	—
A.W.†	F 58	Central	Impaired	Intermittent hypertension	Yes	Yes	Yes	Yes	2.0	No	—

Data generously contributed by:
* Dr. Frederic Bartter, Bethesda, Maryland.
† Dr. Monte A. Greer, Portland, Oregon.

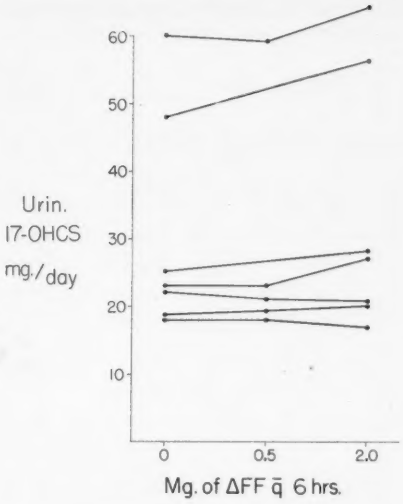

FIG. 5. Urinary 17-hydroxycorticoid excretion in patients with Cushing's syndrome due to autonomous adrenocortical tumors. Left: average basal levels. Middle: values observed during attempted suppression with ΔFF or dexamethasone in a dosage of 0.5 mg. every six hours. Right: values observed during attempted suppression with ΔFF or dexamethasone in a dosage of 2.0 mg. every six hours.

presented the data on 14 patients with equivocal evidence of Cushing's syndrome. In these cases the clinical evidence alone was not strongly suggestive of the syndrome. In all 14 patients the control levels of urinary 17-hydroxycorticoids were above the usual normal range, but small dosages of ΔFF suppressed the 24-hour urinary 17-hydroxycorticoid excretion to less than 4 mg., and in some to less than 2 mg. In view of the uncertainty of the diagnosis in these cases it was decided that treatment should be withheld and that the patients should be observed periodically in the hope that the diagnosis might become clearer with time. In 4 cases serial tests have been possible. With time, the basal levels of 17-hydroxycorti-

SYNDROME DUE TO ADRENOCORTICAL TUMORS

Hirsutism	Weakness	Urinary 17-ketosteroids (mg./24 hrs.)	Urinary 17-hydroxycorticoids (mg./24 hrs.)				Comments
			Basal	1st day of ACTH, 50 units i.v., 8 hrs.	2nd day of ΔFF, 0.5 mg. q. 6 hrs.	2nd day of ΔFF, 2.0 mg. q. 6 hrs.	
—	No	9	25	54	—	28	Adrenocortical adenoma.
Moderate	No	45	17	21	20	—	Excellent response to removal of adrenocortical carcinoma.
—	Yes	33	22	26	21	20	Excellent response to removal of adrenocortical adenoma.
Marked	Marked	70	60	62	59	64	Adrenocortical carcinoma.
Moderate	Yes	20	18	65	18	17	Excellent response to removal of adrenocortical adenoma.
Slight	Yes	9	18	19	19	20	Excellent response to removal of adrenocortical adenoma.
No	Yes	12	23	50	23	27	Excellent response to removal of adrenocortical adenoma.
Moderate	Yes	17	48	54	—	56	Adrenocortical carcinoma. Died of metastases.

TABLE 4. DATA ON 14 PATIENTS WITH CLINICALLY DUBIOUS CUSHING'S DISEASE, ELEVATED BASAL

Patient	Sex & Age	Obesity	Glucose tolerance	Blood pressure (mm.Hg)	Osteoporosis	Ecchymoses	Striae	Edema	Serum K^+ (mEq./L.)	Emotional instability	Oligo-amenorrhea
1.-M.B.	F 30	Central & general	Impaired	135/80	—	No	No	No	4.3	No	No
2.-T.C.	M 17	Massive	Normal	170/100	No	No	Yes	No	4.9	No	—
	17	General	—	130/82	—	No	Diminished	No	—	No	—
3.-R.E.	M 34	Central & general	Impaired	180/100	No	No	No	No	4.9	No	—
	34	Central & general	Impaired	180/100	—	No	No	No	—	No	—
	35	Central & general	Impaired	134/84	No	No	No	No	4.8	No	—
	37	Central & general	Impaired	134/82	No	No	No	No	4.6	No	—
4.-M.H.	F 42	General	Diabetes	175/95	Slight	No	No	No	—	No	No
5.-L.H.	M 18	General	—	120/70	No	No	Yes	No	—	No	—
6.-C.J.	M 43	Central & general	Impaired	181/100	No	No	No	No	4.4	Yes	—
7.-C.La.	F 38	General	Diabetes	160/100	No	No	No	No	4.6	No	No
8.-C.Le.	M 16	General	—	140/85	No	No	Yes	No	—	Yes	—
9.-A.L.	M 50	General	Normal	140/90	No	No	No	No	5.0	Yes	—
10.-M.M.	F 25	General	Impaired	130/70	No	No	No	No	4.1	Yes	Yes
	27	General	Normal	120/78	No	No	No	No	4.3	Yes	Yes
11.-J.M.	M 15	General	Normal FBS	150/80	No	No	No	No	—	No	—
	16	General	Normal FBS	110/70	No	No	No	No	—	No	—
12.-C.P.	M 16	Massive	Normal	170/110	No	No	Yes	No	4.6	Yes	—
13.-J.R.	F 17	Massive	Normal FBS*	120/80	No	No	Yes	No	—	No	Yes
14.-H.W.	M 51	General	Impaired	260/150	No	No	No	No	4.5	No	—

* Fasting blood sugar level.

coid excretion have fallen to normal in all 4 cases. In none of the 14 cases has there been progression to unequivocal Cushing's syndrome.

Effects of unilateral adrenalectomy upon pituitary-adrenal suppressibility in patients with bilateral adrenocortical hypersecretion

Six cases of bilateral adrenocortical hypersecretion were studied following removal of one adrenal gland (Table 5). In one patient (R.J.), "95 per cent" of the second adrenal was also removed. In another patient (E.W.), a benign adenoma 2 centimeters in diameter was found within the hyperplastic adrenal removed at operation.

All 6 patients exhibited resistance to ACTH-suppression following subtotal adrenalectomy—a resistance which was indistinguishable from that observed in patients who had never been subjected to such a procedure. Three patients in this series were subjected to ACTH-suppression tests both before and after unilateral adrenalectomy; no change in suppressibility was observed following the operation. In no case did unilateral adrenalectomy alone bring about any significant decrease in the *basal* levels of 17-hydroxycorticoid excretion. There was no clinical improvement in the

17-HYDROXYCORTICOID EXCRETION, AND NEARLY NORMAL PITUITARY-ADRENAL SUPPRESSIBILITY

Hirsutism	Weakness	Urinary 17-ketosteroids (mg./24 hrs.)	Urinary 17-hydroxycorticoids (mg./24 hrs.)				Comments
			Basal	1st day of ACTH, 50 units i.v., 8 hrs.	2nd day of ΔFF, 0.5 mg. q. 6 hrs.	2nd day of ΔFF, 2.0 mg. q. 6 hrs.	
Moderate	No	10	13	57	2		
—	No	17	18	44	4	—	Studied in May 1959. Wt. 290 lbs.
—	No	—	8	—	2	—	Re-studied in December 1959. Wt. 195 lbs.
—	No	28	17	100	4	—	Studied in January 1957. Wt. 221 lbs.
—	No	19	13	69	3	—	Re-studied in May 1957. Wt. 219 lbs.
—	No	18	12	37	4	—	Re-studied in July 1958. Wt. 215 lbs.
—	No	12	14	39	2	—	Re-studied in October 1959. Wt. 207 lbs.
No	No	9	13	80	2	—	
—	No	16	13	56	2	—	
—	No	12	12	51	3	—	
No	No	10	12	—	2	—	
—	No	10	15	32	1	—	
—	Yes	10	14	—	3	—	
Moderate	No	28	13	62	2	2	Studied in February 1957. Wt. 210 lbs.
Moderate	No	14	10	35	2	—	Re-studied in February 1959. Wt. 201 lbs.
—	No	12	15	40	1	—	Studied in October 1959. Wt. 220 lbs.
—	No	12	9	36	—	—	Re-studied in December 1959. Wt. 215 lbs.
—	No	5	14	—	3	—	
No	No	24	13	—	1	—	
—	No	11	13	—	4	—	

patients in whom the sole therapeutic procedure was unilateral adrenalectomy.

Effects of irradiation of the pituitary upon pituitary-adrenal suppressibility

Of the 27 patients with Cushing's syndrome and bilateral adrenal hypersecretion, 18 were treated initially by irradiation of the pituitary. Ten showed no lasting improvement, as judged by clinical criteria or by the basal levels of 17-hydroxycorticoid excretion. Of these 10 unimproved patients, all exhibited continuing "relative" resistance to the suppressive influence of ΔFF. Eight patients exhibited clinical remissions, and their urinary 17-hydroxycorticoids fell to normal levels following pituitary irradiation. Six of these 8 successfully treated patients were subjected to ACTH-suppression tests during the post-irradiation period (Table 6). In 3 of the 6 patients, normal pituitary-adrenal suppressibility was observed following irradiation therapy. In the other 3, abnormal resistance to the suppressive influence of ΔFF was still observed in the post-irradiation period, although in 2 the resistance to suppression was less than that observed prior to irradiation. These observations suggest that, whereas the

TABLE 5. RESULTS OF ACTH-SUPPRESSION TESTS FOLLOWING UNILATERAL ADRENALECTOMY IN 6 PATIENTS WITH CUSHING'S SYNDROME DUE TO BILATERAL ADRENOCORTICAL HYPERSECRETION

Patient	Date of unilat. adrenalectomy	Date of test	Urinary 17-hydroxycorticoids (mg./24 hrs.)			
			Basal	1st day of ACTH, 50 units i.v., 8 hrs.	2nd day of ΔFF, 0.5 mg. q. 6 hrs.	2nd day of ΔFF, 2.0 mg. q. 6 hrs.
1.—H.B.	Jan. 12, 1957	Jan. 3–9, 1957	20	69	16	3
		Feb. 1957	26	44	16	—
		March 1957	23	—	15	—
2.—R.B.	Jan. 1956*	Dec. 1956	10	20	8	2
3.—V.C.	1949	1959	23	42	16	5
4.—F.E.	June 1956	Sept. 1956	19	49	16	7
		May 1957	19	49	13	10
		Sept. 1957	19	46	19	—
5.—R.J.	Sept. 1956†	Aug. 1956	28	65	21	7
		Oct. 1957	13	12	8	5
		May 1958	14	—	—	5
		Aug. 1958	14	—	—	3
		Jan. 1959	17	14	—	7
6.—E.W.	Apr. 12, 1957	March 1957	17	77	8	7
		May 1957	15	32	8	5

* Unilateral adrenalectomy followed by pituitary irradiation.
† Total removal of left adrenal plus "95 per cent" removal of right adrenal.

basic disorder leading to resistance to ΔFF may be modified favorably by pituitary irradiation, it is also possible to bring about a therapeutic response without correction of the resistance to ΔFF.

Pituitary-adrenal suppressibility in patients with pituitary tumors

Unlike adrenocortical tumors, pituitary adenomas are not associated with *absolute* resistance to the suppressive influence of ΔFF. Of the present series of patients with Cushing's syndrome, 4 had x-ray evidence of enlargement of the sella turcica. In all 4 cases, though there was abnormal resistance to the suppressive influence of small doses of ΔFF, there was definite suppression of pituitary-adrenal function during treatment with large doses. This suggested that, whereas the pituitary adenoma was *associated* with a disturbance in ACTH homeostasis, the ACTH-secreting mechanism had not become autonomous. It was still influenced by corticosteroids.

TABLE 6. RESULTS OF ACTH-SUPPRESSION TESTS BEFORE AND AFTER SUCCESSFUL TREATMENT OF CUSHING'S SYNDROME BY MEANS OF PITUITARY IRRADIATION

Patient	Date of irradiation	Date of test	Urinary 17-hydroxycorticoids (mg./24 hrs.)			
			Basal	1st day of ACTH, 50 units i.v., 8 hrs.	2nd day of of ΔFF, 0.5 mg. q. 6 hrs.	2nd day of ΔFF, 2.0 mg. q. 6 hrs.
1.—R.B.	Jan. 1956	Dec. 1956	10	20	8	2
2.—T.D.	Sept. 1957	June 1957	10	25	7	1
		July 1957	11	—	6	2
		Aug. 1957	12	32	7	2
		Feb. 1958	3	23	—	—
		Feb. 1959	4	—	1	—
3.—B.M.	July 1957	June 1957	17	61	7	2
		Feb. 1958	17	49	2	2
		Feb. 1960	10	—	2	—
4.—T.N.	July–Aug. 1957	June 1957	19	72	19	4
		Aug. 1957	18	55	6	—
		Nov. 1957	3	19	—	—
		June 1958	6	—	2	—
		July 1959	8	37	3	—
5.—M.S.	Feb.–Mar. 1958	Feb. 1958	16	59	8	5
		June 1958	10	45	5	3
6.—E.W.	May 1957*	March 1957	17	77	8	7
		May 1957	15	32	8	5
		June 1957	6	24	6	1
		Aug. 1957	12	26	8	—
		Aug. 1958	7	21	4	2

* Unilateral adrenalectomy April 12, 1957.

In addition to patients included in this study because they were suspected of having Cushing's syndrome, 12 other patients with pituitary tumors but without clinical features of Cushing's syndrome were studied. All 12 subjects had normal basal levels of urinary 17-hydroxycorticoids. Eight exhibited normal pituitary-adrenal suppressibility. The other 4 exhibited abnormal resistance to the suppressive influence of small doses of ΔFF, but none of them showed absolute resistance to large doses of ΔFF.

DISCUSSION

Results of present study as related to those previously reported

The rationale of the ACTH-suppression test as a means of distinguishing between ACTH-dependent hyperadrenocorticism and autonomous hyper-

adrenocorticism is not new. Bartter *et al.* (15) and Wilkins *et al.* (16) demonstrated that adrenal androgens (and 17-ketosteroids) were easily suppressible with cortisone in patients with virilizing congenital adrenal hyperplasia. Jailer *et al.* (17) and Segaloff *et al.* (18) subsequently demonstrated that patients with virilizing adrenocortical tumors differed from those with hyperplasia in that their 17-ketosteroid excretion could not be suppressed with cortisone or cortisol. Less consistent results were obtained, however, when these and other investigators turned from virilizing adrenal disorders to Cushing's syndrome.

Jailer *et al.* (17), administering cortisone in a dosage of 200 mg. per day for four to five days, noted a significant decrease in urinary 17-ketosteroid excretion in 5 of 6 patients with Cushing's syndrome and adrenal "hyperplasia" but no alteration of the elevated 17-ketosteroid excretion in 3 patients with adrenal tumors.

Laidlaw *et al.* (19), administering 5 mg. of 9α-fluorocortisol twice daily for four days to 3 patients and 25 mg. daily for three days to 1 patient with Cushing's syndrome and adrenal hyperplasia, failed to demonstrate a significant decrease in either 17-ketosteroid or 17-hydroxycorticoid excretion. However, Cope and Harrison (20, 21) in a study of 3 cases of Cushing's syndrome associated with adrenal hyperplasia and 1 associated with adrenocortical carcinoma noted that, in response to 9α-fluorocortisol in divided doses totalling 5 to 10 mg. per day, all 3 patients with adrenal hyperplasia exhibited partial suppression of urinary corticosteroid excretion whereas the patient with carcinoma did not. Jenkins and Spence (22), employing 9α-fluorocortisol in dosages of 1 mg. or 2.5 mg. every six hours for two or three days, demonstrated partial suppression of urinary 17-hydroxycorticoid excretion in 2 of 3 patients with Cushing's syndrome and adrenal hyperplasia. Nabarro *et al.* (23), using 9α-fluorocortisol in dosages of 10 to 20 mg. *per day*, demonstrated partial suppression of urinary 17-hydroxycorticoid excretion in 4 of 9 patients with Cushing's syndrome due to bilateral adrenocortical hypersecretion but failed to demonstrate suppression of steroid excretion in 2 patients with Cushing's syndrome due to adrenal tumor.

Gennes *et al.* (24), employed ΔFF as the suppressive agent in a dosage of 2 to 4 mg. per day. They found that urinary steroid excretion was abnormally resistive to suppression in a patient with Cushing's syndrome due to adrenal hyperplasia, but distinct suppression occurred when the dose of ΔFF was increased to 6 mg. per day.

Lipsett and Bergenstal (25) observed that Δ^1,6α-methyl-9α-fluoro-21-desoxycortisol in fractional doses totalling 20 mg. per day partially suppressed urinary 17-hydroxycorticoid excretion in a patient with Cushing's syndrome due to bilateral adrenocortical hyperplasia.

These apparently conflicting reports can easily be reconciled with the observations of the present study when the following facts are considered: 1) that 9α-fluorocortisol is only about one-third as potent as ΔFF with respect to ACTH-suppression, 2) that urinary 17-ketosteroid excretion does not fall during suppression of ACTH as readily as does 17-hydroxycorticoid excretion, and 3) that graded dosages of highly potent suppressors of ACTH have not been used in any sizable series of cases with the dual purpose of confirming the diagnosis of Cushing's syndrome and differentiating ACTH-dependent from autonomous hyperadrenocorticism. Results of the present study indicate that, when performed under carefully controlled conditions, the ACTH-suppression test can be a reliable diagnostic procedure. The use of small doses of ΔFF aids in separating patients with Cushing's syndrome from those without this disease. The use of large doses of ΔFF aids in separating patients with ACTH-dependent Cushing's syndrome from those with autonomous adrenocortical tumors.

Various patients with Cushing's syndrome due to bilateral adrenocortical hypersecretion exhibit different degrees of resistance to the suppressive action of ΔFF. Although the doses of ΔFF arbitrarily selected for this study are highly useful in diagnosis, it is conceivable that extreme cases may yet be encountered in which normal suppression of ACTH will be observed with the 0.5-mg. dosage of ΔFF, or complete resistance to suppression will be observed with the 2.0 mg. dosage. Apparently, however, these extremes are rare and do not seriously limit the practical utility of the standard ACTH-suppression test as a diagnostic tool.

Physiologic significance of "relative resistance" to suppression of ACTH

In addition to its practical value as a diagnostic tool, the ΔFF test is also of heuristic value in clarifying the pathogenesis of Cushing's syndrome. It must be recognized that with the ΔFF test one is not actually distinguishing adrenal hyperplasia from adrenal tumor; rather, one is distinguishing ACTH-dependent hyperadrenocorticism from autonomous adrenocortical hypersecretion. The only way in which corticosteroids are known to suppress adrenal function is through suppression of ACTH secretion by the pituitary. Therefore, whenever ΔFF causes a fall in adrenal steroid secretion one can assume that the adrenal steroid secretion was ACTH-dependent. The fact that large doses of ΔFF consistently induced a decrease in the urinary excretion of 17-hydroxycorticoids in patients with Cushing's syndrome and bilateral adrenal hypersecretion can only mean that these patients were secreting ACTH. If they were secreting ACTH in spite of supraphysiologic levels of cortisol, then it must be inferred that their ACTH-secreting mechanisms were abnormal.

Recent studies in this laboratory have shown that, in patients who have

undergone bilateral adrenalectomy for Cushing's "hyperplasia," blood ACTH levels are not suppressed by dosages of cortisol which consistently suppress ACTH in patients with simple Addison's disease (26).

Pituitary tumors and Cushing's syndrome

Although it has been known for many years that Cushing's syndrome may be associated with pituitary tumors large enough to erode the sella turcica (27–29), there has recently been new interest in this association as a result of the studies of Nelson *et al.* (30) demonstrating high blood levels of ACTH in patients with pituitary adenomas who had previously undergone bilateral adrenalectomy for Cushing's syndrome. In the present study, patients with pituitary adenomas and Cushing's syndrome could not be distinguished from those having bilateral adrenocortical hypersecretion *without* evidence of pituitary adenoma, insofar as suppressibility of pituitary-adrenal function was concerned. The relationship between the pituitary adenoma and the hypersecretion of ACTH is still subject to conjecture. Perhaps a neurohormone (such as the corticotropin-releasing factor (31) of the hypothalamus) acts on the pituitary to induce both hypersecretion of ACTH and formation of the adenoma within the pituitary gland. The primary disorder in Cushing's syndrome with bilateral adrenal hypersecretion could, hypothetically, reside in the abnormal secretion of this neurohormone. Regardless of the explanation, it is apparent from the present study that pituitary tumors associated with Cushing's syndrome do not have the same degree of functional autonomy exhibited by adrenocortical tumors associated with Cushing's syndrome.

A provocative observation made in the course of our study was that one-third of the patients with pituitary tumors but without clinical or chemical features of Cushing's syndrome showed abnormal degrees of resistance to pituitary-adrenal suppression. It appears that in certain patients with pituitary tumors, then, as well as in many patients with Cushing's "hyperplasia," more exogenous cortisol-like steroid is needed to suppress ACTH than would be predicted on the basis of endogenous cortisol levels. The concept that the rate of ACTH secretion is an inverse function of corticosteroid levels is, therefore, an oversimplification. For this reason one should insist that abnormal resistance to pituitary-adrenal suppression is not by itself sufficient evidence to justify a diagnosis of Cushing's syndrome. To be secure, one must insist on the presence of definite clinical features, elevated levels of cortisol metabolites, and abnormal resistance to pituitary-adrenal suppression before making an unequivocal diagnosis of Cushing's syndrome.

Effect of irradiation of the pituitary upon ACTH suppressibility and "reserve"

Although 60 per cent of patients treated by irradiation of the pituitary experienced no remarkable change in pituitary-adrenal function, 40 per cent of them responded with a decrease in basal corticosteroid excretion to normal levels. These successfully-treated patients also exhibited normal adrenal responsiveness to ACTH. That pituitary-adrenal homeostasis was not necessarily restored to normal, however, was indicated by the fact that 3 of the 6 patients who were adequately studied following therapy still exhibited abnormal resistance to pituitary-adrenal suppression. The paradox of the "irradiation-cured" patient whose basal adrenal function is normal but whose resistance to pituitary-adrenal suppression remains abnormal has been resolved by independent studies of "pituitary reserve" (32). The findings have indicated that following "irradiation-cure" the patient with Cushing's disease has a relatively fixed ACTH-secreting capacity. Not only is his ACTH-secreting mechanism less easily suppressible than normal but it is also less responsive than normal to demands for steroids. Apparently in most cases in which pituitary irradiation effects a "cure" of Cushing's disease, it does so not by restoring ACTH homeostasis to normal but, rather, by impairing the responsiveness of the ACTH-secreting mechanism to a point at which, even with maximum secretory activity, it releases an amount of ACTH which happens to coincide with ordinary physiologic requirements.

Lack of effect of unilateral adrenalectomy upon pituitary-adrenal suppressibility

The futility of unilateral adrenalectomy as a method of treatment in patients with bilateral hyperadrenocorticism is apparent from a consideration of the data presented in Table 5. Although a decrease in total adrenal responsiveness to exogenous ACTH is observed following unilateral adrenalectomy, neither the basal output of cortisol nor the suppressibility of pituitary-adrenal function is affected. These observations indicate that even though the amount of ACTH-responsive tissue has been reduced, the fundamental disorder remains uncorrected. Removal of sufficient adrenal tissue may mean that, even with maximum stimulation of the adrenal remnant, the total adrenal output does not exceed a normal amount. This situation was observed temporarily in one patient (R.J.) following total removal of one adrenal and subtotal removal of the other. The primary disorder of excessive ACTH secretion was not corrected (in fact, supernormal levels of ACTH were measured in this patient's blood) even

though the unwanted effects of excess ACTH were temporarily precluded by removal of ACTH-responsive tissue.

Practical use of the ACTH-suppression test

It will become apparent to anyone working with the ACTH-suppression test that there are a number of pitfalls to be avoided if the test is to yield valid results. Obviously the test can be no more reliable than the laboratory performing the steroid determinations. Competent supervision of the administration of ΔFF is necessary to guard against errors due to faulty treatment schedules. The most troublesome source of error is often that of inaccuracy in making 24-hour urine collections. Close supervision of the patient is advisable, and daily urinary creatinine determinations are recommended as a check on the accuracy of collection. Other steroids should not be substituted for ΔFF or dexamethasone in the standard suppression regimen. 9α-Fluorohydrocortisone, for example, cannot be used as a substitute for ΔFF, since it is only about one-third as potent as ΔFF. It is theoretically possible that a spontaneous decrease in the secretory activity of an adrenocortical tumor might coincide with administration of ΔFF, thus creating the mistaken impression that the hyperadrenocorticism is ACTH-dependent. Under such circumstances, pituitary irradiation might be prescribed for treatment of a patient who actually requires adrenal surgery. As a precaution against this set of circumstances it is recommended that, while patients are undergoing pituitary irradiation, the ACTH-suppression test be repeated once or twice. Repeated decreases in adrenal function coinciding with administration of ΔFF will greatly strengthen the diagnosis of ACTH-dependent Cushing's syndrome.

The importance of precision in the diagnostic evaluation of patients suspected of having Cushing's syndrome can hardly be overemphasized. The prognosis of *untreated* Cushing's syndrome is poor (27), but treatment which is appropriate for true Cushing's syndrome is obviously too drastic for the patient who exhibits some of the features of the syndrome but who lacks true hyperadrenocorticism. Patients with autonomous adrenal tumors obviously require adrenal surgery, but those with ACTH-dependent Cushing's syndrome can be spared the expense and risks of adrenalectomy if they respond well to pituitary irradiation. Such considerations should stimulate a continuing interest in the development of tools to improve diagnostic precision in this area of medicine.

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EFFECT OF PREGNANCY ON THE METABOLIC INFLUENCE OF ADMINISTERED PROGESTERONE

RICHARD L. LANDAU, M.D., E. JURGEN PLOTZ, M.D. AND KATHLEEN LUGIBIHL, A.B.

The Department of Medicine, The Department of Obstetrics and Gynecology and the Argonne Cancer Research Hospital (U. S. Atomic Energy Commission) of the University of Chicago, Chicago, Illinois

ABSTRACT

Three women in the fourth, seventh and eighth months respectively of normal pregnancy were given courses of intramuscularly administered progesterone in a dose of 50 or 100 mg. per day. In none of them was there a detectable influence on protein metabolism. In one, the 100-mg. course appeared to induce a mild natriuresis; no loss of sodium occurred in the others. These results contrast with the moderate catabolic response and distinct natriuresis observed regularly in normal subjects. Approximately 50 mg. daily of administered progesterone had previously been shown to elicit a maximal catabolic response. The failure of progesterone to be catabolic in pregnant women was explained by the assumption that endogenous progesterone was already inducing its maximal catabolic influences. The mild and inconstant natriuretic responses may have resulted from an inability of administered progesterone to inhibit sufficiently the influence of the increased amount of aldosterone present during pregnancy.

IT HAS been shown that intramuscularly administered progesterone will increase the net rate of protein catabolism and enhance the urinary excretion of sodium and chloride in nonpregnant women and in men (1–3). This mild to moderate catabolic process can be distinguished qualitatively from those resulting from excesses of adrenocortical and thyroid hormones (2, 4). The natriuresis and chloruresis have been ascribed to an inhibition of the renal tubular effects of aldosterone and other sodium-retaining adrenal secretions (2, 5). The influence of progesterone on both protein and electrolyte metabolism was detectable when as little as 12.5 mg. per day was administered. The catabolic response was maximal at a daily dosage of about 25–50 mg., but the intensity and duration of the natriuresis continued to increase until a dosage level of at least 200–300 mg. per day had been reached (6).

It appears likely that these metabolic properties of progesterone will prove to be important during pregnancy when very large amounts of the

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hormone are secreted. Estimates based on the fact that about 15 per cent of administered progesterone is excreted as urinary pregnanediol indicate that about 25–75 mg. of progesterone may be secreted each day during the first trimester of pregnancy, with a progressive increase of 200–400 mg. per day before delivery (7, 8). More direct measurements of the rate of progesterone secretion indicate secretory rates of 20 and 41 mg. per day in the first and second trimesters (9), and 190–280 mg. per day in the third trimester (10, 11). From the dose-response relationships noted previously (6), it could be assumed that the pregnant women are under the influence of the maximum catabolic stimulus of progesterone during most of the period of gestation. The progressively increasing rate of progesterone secretion would also be expected to result in greater capacity for inhibition of aldosterone, but the rate of aldosterone secretion also rises during pregnancy (12, 13).

In these circumstances one would anticipate that, after the first few weeks of gestation, administered progeterone would have no effect on nitrogen metabolism, and that its influence on urinary sodium excretion would be dependent in large measure upon the pre-existing balance of endogenous progesterone and aldosterone. As a partial test of these suppositions the metabolic effects of progesterone in a dosage of 50–100 mg. per day was determined in 3 women during the second and third trimesters of pregnancy. Such amounts of progesterone have frequently been administered to pregnant women to prevent abortion (14).

METHODS

The 3 subjects studied were in the fourth, seventh and eighth month of pregnancy, respectively. All of the pregnancies were uncomplicated and without excessive weight gain. The women lived in the metabolic ward of the hospital and consumed adequate constant diets in the usual manner. Urine was collected in 24-hour specimens as soon as sufficient time had elapsed for metabolic equilibration. The 24-hour collections were usually combined in 48-hour pools for analysis. Completeness of collections was checked by urinary creatinine determinations. The urine specimens were also analyzed for total nitrogen, inorganic phosphorus, sodium and potassium by methods previously noted (2). Pregnanediol was determined by the procedure of Bongiovanni and Clayton (15), after glucuronidase hydrolysis and extraction.

Subject B.Pe (Fig. 1) received progesterone in a dosage of 50 mg. per day intramuscularly for eight days; Subjects J.H. (Fig. 2) and D.W. (data not illustrated) were given 100 mg. per day.

RESULTS

In none of these pregnant women was there conclusive evidence that nitrogen excretion was influenced by treatment with progesterone. In Subject B.Pe. (Fig. 1), urinary nitrogen excretion continued at the control level throughout the treatment period. Although nitrogen excretion dropped

slightly at the conclusion of treatment, this can hardly be regarded as evidence of a prior catabolic process. During the seventh month of gestation in Subject J.H. (Fig. 2), 100 mg. of progesterone daily failed to induce even a suggestion of an effect on nitrogen excretion. The excretion of nitrogen was also uninfluenced in Subject D.W. (data not shown). Urinary inorganic phosphorus excretion was likewise unaffected in these subjects. Thus there was no evidence that protein metabolism could be

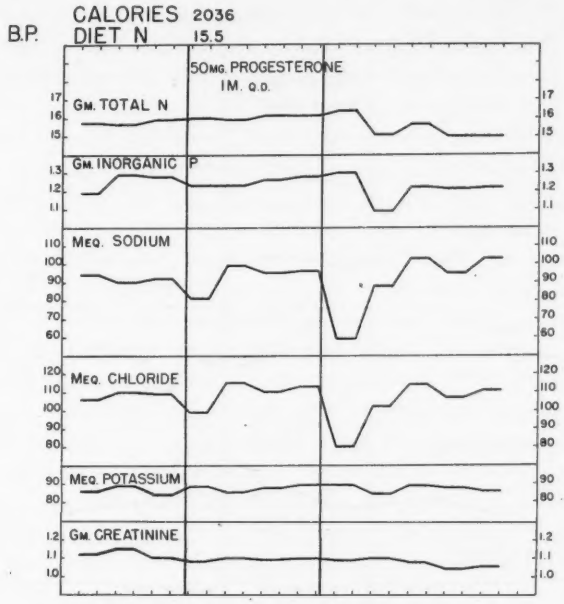

FIG. 1. Effect of progesterone (50 mg. per day) on the urinary excretion of total nitrogen, inorganic phosphorus, sodium, chloride and potassium in Subject B.Pe., a normal woman in the fourth month of pregnancy.

influenced by administered progesterone in the middle or last trimesters of pregnancy.

When examined in the light of other experiences with progesterone, the results obtained in Subject J.H. (Fig. 2) suggest that the 100-mg. dosage of the hormone may have induced a mild sodium diuresis which lasted the first four days of treatment. The estimated sodium loss totaled only 65 mEq., and except for a single low value on the third post-treatment day, there was no distinct post-treatment retention of sodium. In Subject B.Pe. (Fig. 1), 50 mg. of progesterone each day induced no sodium loss, but sodium retention was observed during the first two days after progesterone

was discontinued. In Subject D.W., who also received 100 mg. daily, there was no loss or post-treatment retention of sodium.

The basal body temperatures did not rise during treatment with progesterone in any of the subjects. Pregnanediol excretion in Subject J.H. rose from a pre-treatment level of 58 mg. to a peak of 90 mg. per twenty-four hours, about 10 to 15 per cent of the administered progesterone being recovered as pregnanediol. In the other 2 women the course of pregnanediol

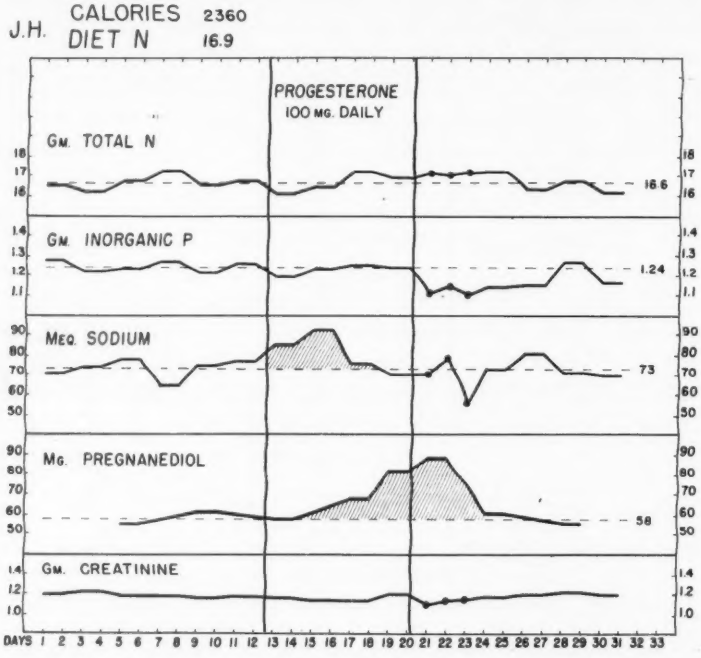
J.H.
CALORIES 2360
DIET N 16.9
PROGESTERONE
100 MG. DAILY
GM. TOTAL N
16.6
GM. INORGANIC P
1.24
MEQ. SODIUM
73
MG. PREGNANEDIOL
58
GM. CREATININE
DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33

FIG. 2. Effect of progesterone (100 mg. per day) on the urinary excretion of total nitrogen, inorganic phosphorus, sodium and pregnanediol, in Subject J.H., a normal woman in the seventh month of pregnancy. Broken horizontal lines indicate the control levels (averages); significant changes are indicated by cross-hatched areas.

excretion during treatment was not followed in such detail, but in each case the excretion increased as a result of progesterone therapy.

DISCUSSION

These failures of administered progesterone to enhance urinary nitrogen excretion were the first to be observed in about 75 such studies in men and women under a variety of circumstances. On the assumption that endogenous progesterone acts like the administered hormone, this lack of re-

spone had been anticipated. As noted previously, 50 mg. of progesterone per day usually induced the maximum catabolic effect. These 3 pregnant women were almost certainly under the influence of at least that quantity of endogenous progesterone when treatment was started (urinary pregnanediol excretions were 14, 58 and 45 mg. per twenty-four hours, respectively). The negative results are accordingly consistent with, and indeed support, the view that during the latter two-thirds of pregnancy progesterone is exerting its maximal catabolic influence.

These studies also provide controls of a sort for the numerous instances in which progesterone did act as a catabolic agent. The remote possibility that in some manner the mild inflammatory reaction sometimes noted at the site of progesterone injection could have accounted for the catabolic response had been considered. However, the failure of progesterone to enhance nitrogen excretion during pregnancy, when the potential for local irritation was as great as ever, would seem to eliminate this consideration. Thus the concept that the enhancement of protein catabolism is a physiologic influence of the hormone has been strengthened.

The conclusion that during pregnancy—a time of fetal and selective maternal growth—protein catabolism of the maternal organism as a whole is being enhanced by one of the principal female hormones is indeed surprising. To be sure, estrogens are anabolic (16, 17), and the two female hormones may thus counteract each other. Recent studies have suggested that the catabolic influence of progesterone is not exerted directly upon peripheral tissues but, rather, is the result of an acceleration of amino-acid utilization by the liver (18). If this be the case, this influence of progesterone would probably have a less obvious significance in the economy of the organism than the mere balancing of the effect of the anabolic estrogens.

The importance of progesterone in the regulation of electrolyte and water metabolism during pregnancy is more apparent. The huge quantities secreted in pregnancy have generally been thought to be required primarily for the preservation of the placenta and an optimum state of myometrial contractility. However, the fact that progesterone is a potent inhibitor of the sodium-retaining action of aldosterone would seem to assign to it a key position in the hormonal regulation of urinary sodium excretion during pregnancy as well. If the amount of aldosterone secreted throughout pregnancy were relatively constant, the rising rate of progesterone secretion would probably induce a serious sodium diuresis like that observed when progesterone is administered to adrenal-deficient patients managed with constant doses of aldosterone or desoxycorticosterone (2). Accordingly the enhancement of aldosterone secretion which occurs during pregnancy could reflect, at least in part, a compensatory response to the

inhibitory action of progesterone. It is also possible, however, that this increased secretion of aldosterone is causally related to other phenomena.

The minimal natriuresis induced by progesterone in Subject J.H. (Fig. 2) and the absence of a significant loss of sodium in the other 2 subjects suggest that insufficient aldosterone was inhibited to induce a deficiency of mineral corticoids. This suggestion implies that there is more unopposed aldosterone circulating or very readily available in the pregnant organism than in other normal subjects who have been studied. It is also appreciated, however, that other endocrine and metabolic changes could impair the natriuretic response to progesterone. In physiologic amounts, estrogen does not interfere with the natriuresis (19), but other possibilities have not been investigated.

It is thus possible that the enhancement of aldosterone secretion in pregnancy is not merely a compensatory reaction to the large quantity of circulating progesterone. In this circumstance it would not be unreasonable to propose that endogenous progesterone plays a dynamic role in the daily regulation of salt metabolism by inhibiting the action of possible excesses of adrenal salt-retaining hormones.

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BILIARY AND URINARY METABOLITES OF 4-C^{14}-PROGESTERONE IN HUMAN SUBJECTS*

EDWARD CHANG, PH.D., W. ROY SLAUNWHITE, JR., PH.D. AND AVERY A. SANDBERG, M.D.

Roswell Park Memorial Institute, Buffalo 3, N. Y.

ABSTRACT

C^{14}-progesterone was injected intravenously into 9 human subjects, 4 of whom had biliary fistulas. Following hydrolysis of steroid conjugates and continuous extraction with ether, the pooled urinary and pooled biliary extracts contained more than 50 per cent of the injected radioactivity. The extracts were separated into several fractions by counter-current distributions, followed by adsorption chromatography. Radioactive metabolites eluted from alumina columns were characterized by isotope dilution with standard carriers in addition to chromatographic mobilities. Pregnanediol, allopregnanediol, pregnanolone and progesterone were identified in both urine and bile. Results indicate that hydroxylated metabolites of progesterone are eliminated mostly in the urine, while the corresponding ketonic compounds are excreted chiefly in the bile.

INTRODUCTION

THE principal pathway of the metabolism of progesterone is believed to be progesterone→pregnanedione→pregnanolone→pregnanediol,[1] although small amounts of the corresponding allopregnane compounds are formed (1). It is important to note, however, that these conclusions are based on a recovery of only 15–30 per cent of administered progesterone as urinary metabolites. More recent experiments with C^{14}-progesterone have indicated that one reason for the low recovery of metabolites in the urine is that substantial amounts enter the feces by way of the bile (2–5). For example, following the intravenous injection of 4-C^{14}-progesterone into human subjects with bile fistulas, Sandberg and Slaunwhite (4) found that nearly 30 per cent of the radioactivity was excreted in the bile while 50 per cent was excreted in the urine. In normal subjects, 13 per cent of the injected radioactivity was excreted in the feces.

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[1] Pregnanediol = 5β-pregnane-3α,20α-diol.
Allopregnanediol = 5α-pregnane-3α,20α-diol.
Pregnanolone = 5β-pregnan-3α-ol-20-one.
Pregnanedione = 5β-pregnane-3,20-dione.

Identification of biliary metabolites has been accomplished only recently. Wiest *et al.* (5) identified C^{14}-pregnanolone and C^{14}-pregnanediol in biliary extracts after administration of 4-C^{14}-progesterone.

In this communication we wish to report an analysis of urinary and biliary excretory products following the injection of 4-C^{14}-progesterone into human subjects (4).

METHODS

Radioactive extracts. The material used in this study, as previously reported (4), was obtained after intravenous injection of 1–2 μc. of 4-C^{14}-progesterone (5 μc. per mg.) into 4 males and 5 females. Three females and 1 male had bile fistulas. All of the urinary extracts were pooled, as were all of the biliary extracts. Each extract, dissolved in ether, was washed with saturated sodium bicarbonate and water and evaporated to dryness.[2]

Counter-current distribution. The pooled urinary extracts were separated into three groups by counter-current distribution with 50 transfers, using the system benzene-50% aqueous methanol (system I). Due to the excessive formation of emulsion, preliminary separation of the biliary sample in this system was not satisfactory. The separated groups of the urinary extracts and the entire bile sample were again distributed in another solvent system, namely, 50% ethyl acetate, 50% cyclohexane-70% aqueous methanol (system II) with 99 transfers. The distribution curve obtained by plotting the radioactivity against the tube number showed several peaks. A fairly good resolution was achieved by this system, but there was no separation of compounds isomeric at C-5. The subsequent separation of pregnanes from allopreganes was accomplished, however, by column chromatography.

Column chromatography. The chromatography column, made of 1×25 cm. Pyrex tubing with a fritted glass plate of fine porosity for support, was packed with a slurry of 10 grams of neutral aluminum oxide (Woelm, grade I) in benzene. Approximately 50 ml. of redistilled benzene was allowed to percolate through the column before the sample was introduced. The sample was first dissolved in 1 milliliter of absolute ethanol. The alcohol solution was then absorbed onto several filter-paper discs (Whatman No. 40, punched by No. 5 cork borer, 1 cm. in diameter). After placing the paper discs on top of the column and pressing out the air bubbles, they were covered with a little absorbent. The column was eluted with 250 ml. of each of the following solvents: benzene, and 0.2, 0.4, 0.6, 0.8, 1.0, 5.0 and 10 per cent ethanol in benzene. Positive nitrogen pressure was applied to the column to insure a constant rate of solvent flow at approximately 4 ml. per minute. Fractions of 10 ml. or 20 ml. were collected by an automatic fraction collector. With authentic standards, this column was capable of separating pregnanolone from allopregnanolone and pregnanediol from allopregnanediol.

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[2] The radioactivity present in the washed urinary and biliary extracts (Figs. 1 and 4) represents the counts on material extractable with organic solvents from the urine and the bile following hydrolysis with β-glucuronidase and other procedures (4). Approximately 30 per cent of the injected C^{14}-progesterone and its metabolites is extractable from the urine (containing 50 per cent of the total counts) with these procedures (4), in contrast to less than 7 per cent extractable from the bile (containing 30 per cent of the total counts). Only an aliquot of the combined urinary extracts was used in the experiment outlined in Figure 1, whereas in the case of bile the total combined extracts were used.

Carrier crystallization. In order to identify further the isolated radioactive metabolites, isotopic dilution technique was employed. The standard material used as carrier was first recrystallized from aqueous methanol. The recrystallized carrier was then added to the isolated metabolites. The identification was considered complete when there was no change in specific activity following successive recrystallizations.

Paper chromatography. Paper chromatography was carried out in cases in which there was some doubt regarding the homogeneity of the metabolite eluted from the alumina column. The metabolite(s) was adsorbed on Whatman No. 2 paper strips (1×43 cm.); appropriate standards were placed on adjoining strips. Following equilibration for an hour and a half, chromatograms were developed for six hours at 25° C. in a glass tank using 90 per cent cyclohexane and 10 per cent benzene as the moving phase and 80 per cent aqueous methanol as the stationary phase. The sample strip was then cut into 43 pieces, each covering an area of 1 sq. cm. The radioactivity was eluted from these areas by soaking in 4 ml. of absolute ethanol overnight. An aliquot was plated and the radioactivity determined. Nonradioactive standard spots were visualized by spraying the paper with suitable color reagents.

Reduction and dehydration. Various attempts at the separation of progesterone and pregnanedione were unsatisfactory. Mobilities of these two compounds on either the alumina column or by paper chromatography were fairly similar, making the isolation of a pure fraction impractical. Hence, the compounds were modified so as to facilitate their chromatographic separation. The ketones at C-3 and C-20 were reduced with sodium borohydride and the enol produced from progesterone was dehydrated in acid solution to form a diene.

Standard progesterone (10 mg.) and pregnanedione (10 mg.) were added to the samples containing compounds with mobilities similar to those of the standards. The mixture was dissolved in 20 ml. of methanol and then chilled to 0–5° C. To the chilled mixture, 10 ml. of methanolic sodium borohydride (1 mg. sodium borohydride/1 ml. of methanol) was added, with thorough mixing. The mixture was then allowed to react for three hours. At the end of the reaction period, 1–2 drops of glacial acetic acid were added and the mixture was poured into 100 ml. of cold water containing 2 ml. of acetone. After standing overnight at 0° C., the aqueous solution was subjected to extraction with ether. The ether phase was washed with 2.5 per cent sodium carbonate solution and water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure.

The residue, dissolved in 50 ml. of 0.03 *N* alcoholic hydrochloric acid, was refluxed for one hour. The mixture was then cooled to room temperature and partitioned between equal volumes of ether and water (250 ml. of each phase). The ether phase was washed successively with water, sodium carbonate and water until the washing was free of acid. The dry residue was fractionated on an alumina column as previously described.

RESULTS

Urinary metabolites

Preliminary counter-current distribution of the urine extract in solvent system I (n = 50) separated the metabolites into three groups. More than 90 per cent of the radioactivity was found in tubes 32–46(U-III) and tubes 12–30 (U-II); the remaining radioactivity was in tubes 2–12 (U-I). Redistribution of fraction U-III in system II showed a further separation into six bands. Distribution of standard compounds in the same system indi-

cated that bands U-III-2, U-III-3 and U-III-4 corresponded to pregnandiol, pregnanolone amd progesterone, respectively. A flow diagram of counter-current distributions and chromatography is shown in Figure 1.

Materials in bands U-II, U-III-2 and U-III-3 (Fig. 2) as well as U-III-4 were chromatographed separately on alumina. Metabolites were identified by comparison with standards and by isotopic dilution with carrier. Metabolites identified by recrystallization with added carrier are presented in Table 1.

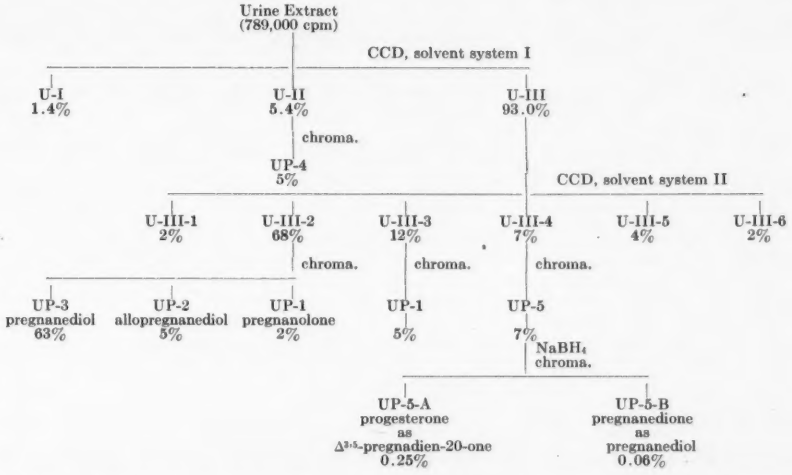

FIG. 1. Summary of the procedure for separation of compounds in the urinary extract. The percentage of radioactivity expressed for each fraction is calculated with respect to the initial washed pooled extract.

Column chromatography of U-III-4 showed the presence of compounds with mobilities similar to those of progesterone and pregnanedione. Results of paper chromatography indicated that U-III-4 contained both progesterone and pregnanedione. This material, mixed with added standards was subjected to reduction and dehydration (*cf.* Methods). The elution curve after chromatography on alumina showed two major peaks (Fig. 3). By comparison with standard compounds, the first peak (UP-5A) corresponded to 3,5-pregnadien-20-ol, and the second peak (UP-5B) corresponded to pregnanediol. The material in peak UP-5A was further identified by recrystallization with added carrier. The lack of superimposibility of ultraviolet absorption and radioactivity curves in peak UP-5A (Fig. 3) as well as the sudden decrease in specific activity on crystallization (Table 1) indicate that this peak was nonhomogeneous.

TABLE 1. IDENTIFICATION OF URINARY AND BILIARY METABOLITES BY CARRIER CRYSTALLIZATION

Radioactive metabolite analyzed	Carrier added	Solvent	Specific activity of crystalline material (counts/min./mg.)				
			Before recryst.	After 1st recryst.	After 2nd recryst.	After 3rd recryst.	After 4th recryst.
UP-1	Pregnanolone (10 mg.)	Methanol	2,427	2,351	2,331	2,235	2,264
UP-2	Allopregnanediol (8 mg.)	Methanol	1,895	2,081	1,737	2,230	
UP-3	Pregnanediol (10 mg.)	Methanol	10,506	9,749	9,384	8,718	9,470
UP-5-A	3,5-pregnadien-20-ol (20 mg.)	Chloroform; pet. ether	127	27	26	29	30
BP-1	Pregnanolone (11 mg.)	Methanol	443	513	566	531	510
BP-2	Allopregnanediol (7 mg.)	Methanol	133	189	184	178	
BP-3	Pregnanediol (12 mg.)	Methanol	1,425	1,320	1,533	1,510	
BP-5	Progesterone (10 mg.)	Ethanol	113	65	58	60	

Biliary metabolites

The biliary extracts were distributed in solvent system II (Fig. 4). Bands B-II, B-III, and B-IV corresponded in position to U-III-2, U-III-3 and U-III-4, respectively. Subsequent column chromatography of these bands showed the presence of progesterone (BP-5), pregnanolone (BP-1), allopregnanediol (BP-2), pregnanediol (BP-3) and an unidentified polar metabolite (BP-4) (Fig. 5). Biliary metabolites identified by chromatographic mobilities and carrier recrystallizations are presented in Table 1.

DISCUSSION

The results obtained with the urinary extract are largely confirmatory of those previously published. Pregnanediol was the major metabolite in the urine, followed by pregnanolone and allopregnanediol. Trace amounts of two closely related compounds, presumably unmetabolized progesterone and pregnanedione, were also found. A compound present in substantial amount (5 per cent) and more polar than pregnanediol has not yet been identified. Allopregnanedione and allopregnanolone have not been identified in the urinary extract but may be present in the chromatographic peaks which remain unidentified due to the lack of suitable standards.

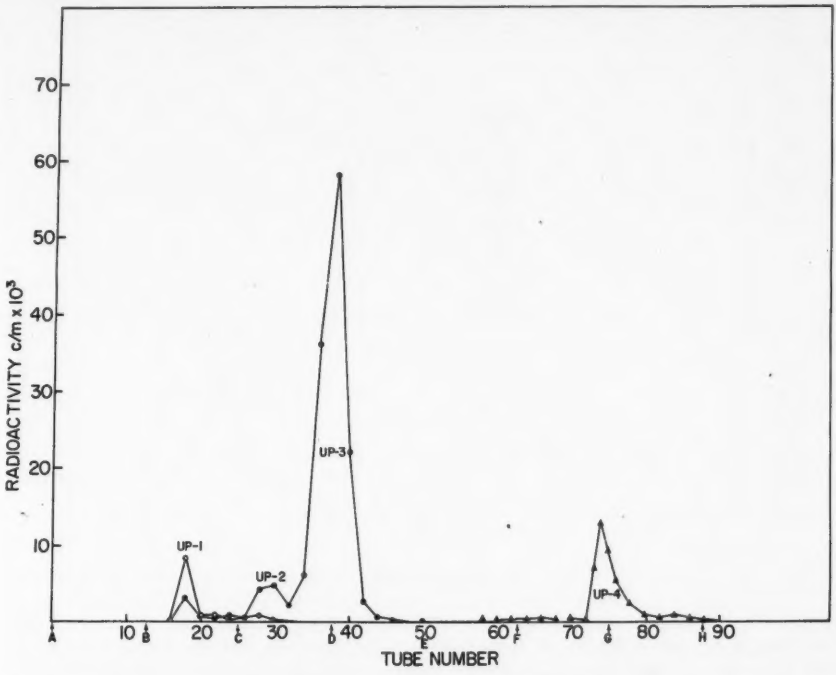

FIG. 2. Column chromatography of U-II (▲—▲), U-III-2 (●—●) and U-III-3 (○—○). Each tube contained 20 ml. Eluants were A, benzene; and B-H, 0.2, 0.4, 0.6, 0.8, 1.0, 5.0 and 10% ethanol in benzene respectively.

Moreover, nothing can be said regarding the possible presence of 3β isomers (1), since these standards were also not available.

Only Wiest *et al.* (5) and Rogers and McLellan (6) have investigated biliary extracts, which are more difficult to process than are urinary extracts. We have confirmed their finding of pregnanediol (5, 6) and pregnanolone (5) and have, in addition, identified allopregnanediol and progesterone. Thus, the steroid pattern of the bile is qualitatively much like that of the urine. On a quantitative basis, however, there is a noticeable difference, the bile tending to contain less of the more hydrophilic or more polar metabolites. For example, metabolites more polar than pregnanediol were reduced from 6.8 per cent in the urine to 2.5 per cent in the bile and the pregnanediols were reduced from 68 per cent to 16 per cent, while pregnanolone and progesterone increased from 7.6 per cent to 12.5 per cent with an additional 23.5 per cent of material of similar polarity remaining unidentified in the bile.

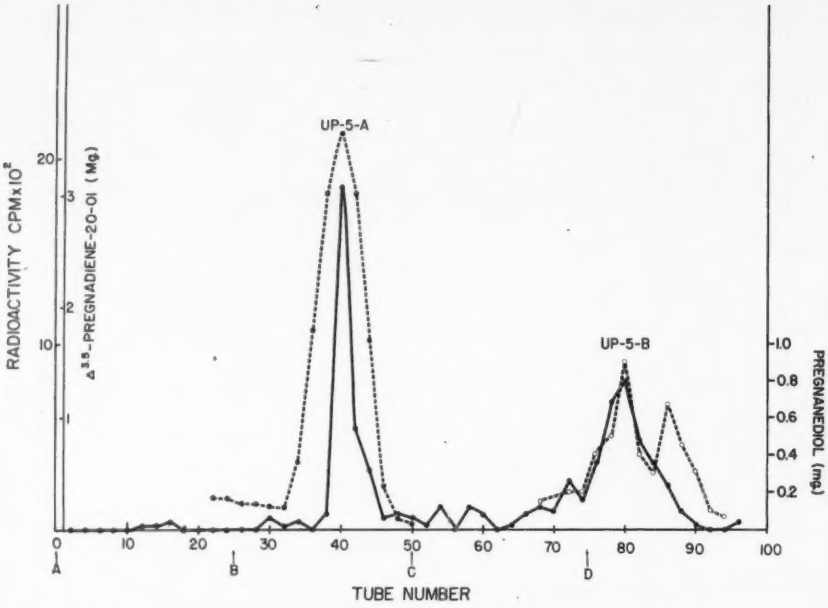

FIG. 3. Column chromatography of UP-5 mixed with 10 mg. each of progesterone and pregnanedione followed by reduction and dehydration. Ultraviolet absorption at 235 mμ. (● – – ●); determination of pregnanediol-like compounds by the vanillin method (unpublished results of E.C.) (○ – – ○); radioactivity (●—●). Each tube contained 10 ml. Eluants were A, B, C and D, as in Figure 2. .

The urinary excretion of progesterone (which is assumed to be unconjugated because of its nonalcoholic nature) may be attributed to glomerular filtration in the kidney, but its excretion in the bile is not so simply explained. To our knowledge, progesterone is the only steroid which occurs in unconjugated form in human bile. This, however, may not be a unique phenomenon, but merely the result of inadequate investigation.

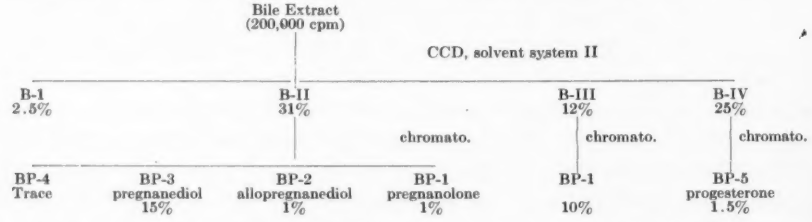

FIG. 4. Summary of procedure for separation of compounds in the bilary extract. The percentage of radioactivity expressed for each fraction is calculated with respect to the initial washed pooled extract.

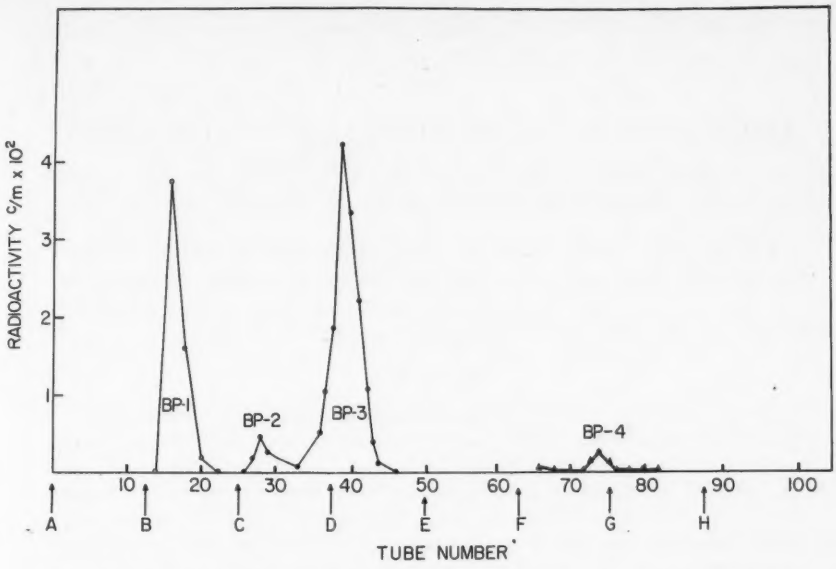

FIG. 5. Column chromatography of B-II (●—●), B-III (○—○) and B-IV (▲—▲). Each tube contained 20 ml. Eluants were A–H as in Figure 2.

Acknowledgments

The authors wish to express sincere appreciation to Misses Barbara Rovner and Margaret Griffith for their technical assistance; to Dr. W. H. Pearlman of the Waldemar Medical Research Foundation for a generous supply of allopregnanediol; and to Dr. Harold L. Upjohn of Upjohn Co. for pregnanolone.

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THE INFLUENCE OF STEROIDS ON URINARY GONADOTROPIN EXCRETION IN A POSTMENOPAUSAL WOMAN*†

EUGENIA ROSEMBERG, M.D. AND IZO ENGEL, M.S.

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts; The Worcester State Hospital, Dementia Praecox Research Project, and The Worcester City Hospital, Worcester, Massachusetts

ABSTRACT

Urinary excretion of human pituitary gonadotropin (HPG) was studied in a postmenopausal subject following the administration of methyltestosterone, conjugated estrogens or norethisterone (17α-ethynyl-19-nortestosterone, Norlutin). HPG excretion was measured by the mouse uterine response, employing estrone as the standard reference material. Daily consecutive assays were made. Methyltestosterone in oral dosages of 5, 25, 50 or 100 mg. daily did not significantly alter HPG excretion. Conjugated estrogens in an oral dosage of 0.25 mg. daily increased HPG excretion on the fifth day of administration; there was a return to control levels immediately after withdrawal of medication. A dosage of 2.5 mg. of conjugated estrogens daily was tested twice with the following results: 1) HPG excretion was completely suppressed within five days but rose to control values thirteen days after cessation of medication; 2) HPG excretion was diminished on the seventh day, and the reduction was maintained until four days after withdrawal of medication. Conjugated estrogens in a dosage of 5 mg. daily diminished HPG excretion on the last day of administration; excretion rose to control levels on the ninth day after cessation of medication. Estrone sulfate in a daily dosage of 2.5 mg. did not significantly alter HPG excretion. Norethisterone (Norlutin) in oral dosages of 5 and 10 mg. daily did not alter HPG excretion; 20 mg. daily caused diminution of HPG excretion on the sixth day of administration, and there was a return to control levels four days after withdrawal of medication.

THE purpose of this study was to investigate the effect of estrogens, methyltestosterone and norethisterone (17α-ethynyl-19-nortestosterone or Norlutin) on pituitary gonadotropic function as reflected in the urinary excretion of human pituitary gonadotropin (HPG).

To provide for a quantitative evaluation of HPG excretion the tech-

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nique of daily consecutive assays, employing estrone as the standard reference material was used. Results are expressed as micrograms of estrone equivalent per twenty-four hours.

MATERIAL AND METHODS

The subject selected for this study was a normal postmenopausal woman, aged 56. HPG excretion levels were followed daily before, during and after the administration of the steroids by the oral route. Urine was collected in 24-hour specimens, using toluene as preservative. Specimens were frozen at −14° C. until processed.

The method for extraction and quantitative estimation of total HPG excretion has been described in previous publications (1, 2).

RESULTS

Control cyclic variation

The HPG excretion pattern in this subject, followed daily for twenty-seven days, is shown in Figure 1.

Negative titers were observed twice. Positive values ranged from 1.97 to 25 μg. of estrone equivalent per twenty-four hours. There was a cyclic variation in excretion; cycles of three, four, five and six days were observed. The magnitude of the daily fluctuation, measured as the span between the lowest and highest values, was 12.7-fold. Partial overlap in confidence

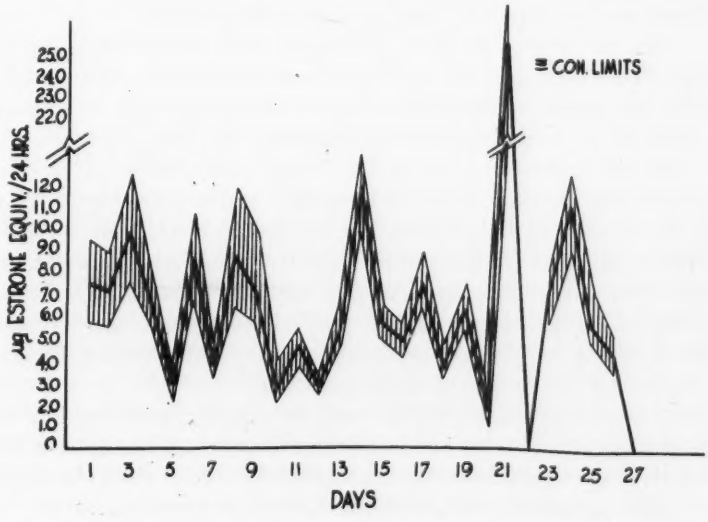

FIG. 1. Daily consecutive assays of urinary HPG in a 56-year-old normal postmenopausal woman, showing cyclic variation.

limits occurred in 5 or 27 assays. The mean of the individual deviations in relative potency, as obtained by the confidence limits of P:0.95, was 19.3 per cent irrespective of the sign.

Table 1 shows the mean excretion values when the period of observation was subdivided into four groups of seven, seven, seven and six days respectively.

Although excretion was cyclic, the mean value for each period did not differ significantly from the mean values for the subsequent periods of observation.

TABLE 1. DAILY CONSECUTIVE HPG ASSAYS IN A 56-YEAR-OLD POSTMENOPAUSAL WOMAN

Period [No. of days]	Mean HPG excretion (μg. estrone equiv./ 24 hrs.) (range)	P*	P**	P***
1 [7]	6.74 (2.93– 9.89)	>0.05<0.1	>0.5	>0.1<0.5
2 [7]	3.44 (2.79–12.10)		>0.1<0.5	>0.5
3 [7]	8.64 (1.97–25.33)			>0.1<0.5
4 [6]	4.35 (0.0 –11.02)			

* P: Significance of difference of mean value against mean value for period 2.
** P: Significance of difference of mean value against mean value for period 3.
*** P: Significance of difference of mean value against mean value for period 4.

Effect of methyltestosterone

Figures 2, 3, 4 and 5 show the effect of the oral administration of 5, 25, 50 and 100 mg. of methyltestosterone, on urinary HPG.

The cyclic variations in HPG excretion were maintained during the administration of methyltestosterone. Three-day and four-day cycles were observed both when methyltestosterone was administered in a dosage of 5 mg. daily for nine days and during the control periods. When the dosage of methyltestosterone was increased to 25 mg. daily, three-day and seven-day cycles were observed, whereas three-day and five-day cycles occurred during the control periods. When the dosage of methyltestosterone was increased to 50 mg. daily for eleven days, four-day and seven-day cycles were observed, and three-day, four-day and seven-day cycles during the control periods. When the dosage of methyltestosterone was increased to 100 mg. daily for ten days, three-day, four-day and five-day cycles were observed during the period of administration.

Table 2 shows the mean HPG excretion values corresponding to the control periods and the periods of methyltestosterone administration.

Mean HPG excretion levels during administration of methyltestosterone did not differ significantly from either the pre- or post-medication control values.

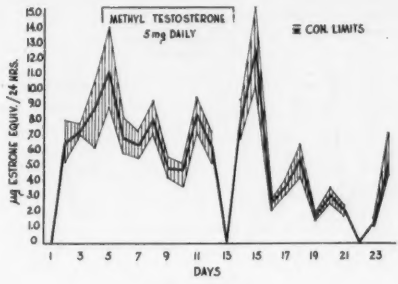

FIGURE 2

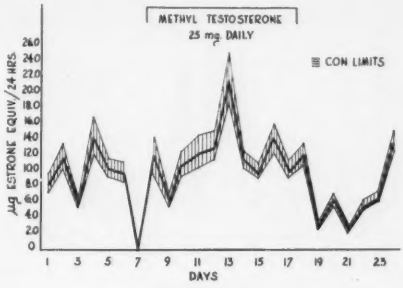

FIGURE 3

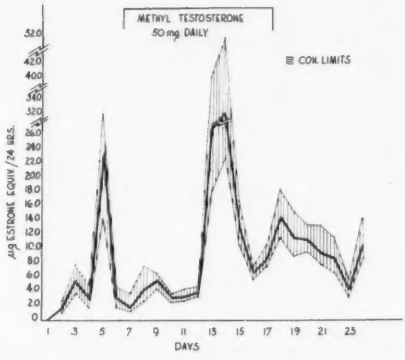

FIGURE 4

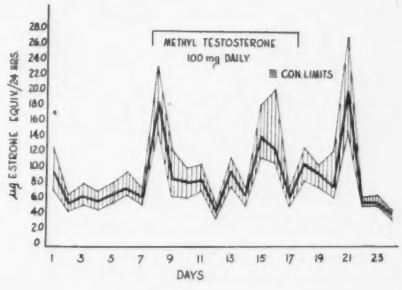

FIGURE 5

FIGS. 2–5. Daily consecutive assays of urinary HPG in a 56-year-old normal postmenopausal woman before, during and after oral administration of methyltestosterone in the following dosages: (Fig. 2), 5 mg. daily; (Fig. 3), 25 mg. daily; (Fig. 4), 50 mg. daily; (Fig. 5), 100 mg. daily.

Effect of estrogens

Conjugated estrogens. Figures 6, 7, 8 and 9 show the effect of oral administration of conjugated estrogens on urinary HPG. Figure 10 shows the effect of oral administration of estrone sulfate. A commercial preparation of conjugated estrogens (equine) was employed; this material is standardized as sodium estrone sulfate.

Although three-day and four-day cycles were observed during the oral administration of 0.25 mg. of conjugated estrogens daily for ten days, as well as during the control periods, the level of HPG excretion on the fourth to the tenth days of administration was much higher than during control periods.

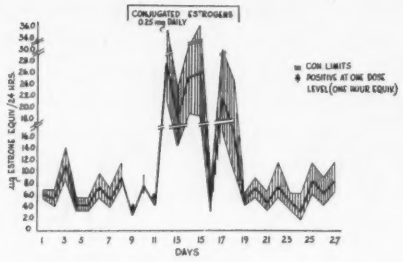

FIGURE 6

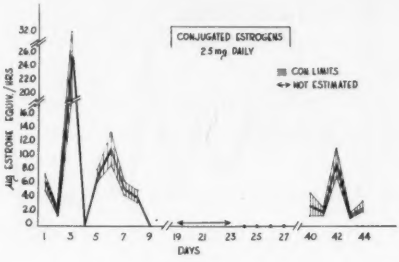

FIGURE 7

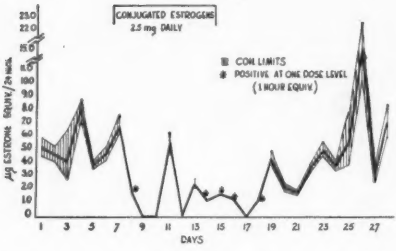

FIGURE 8

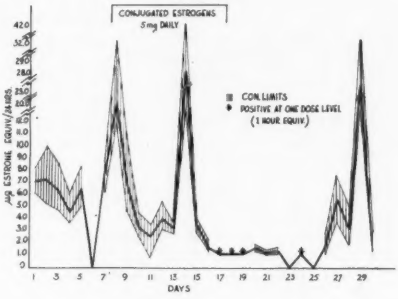

FIGURE 9

FIGS. 6–9. Daily consecutive assays of urinary HPG in a 56-year-old normal postmenopausal woman before during and after oral administration of conjugated estrogens in the following dosages: (Fig. 6), 0.25 mg. daily; (Fig. 7), 2.5 mg. daily; (Fig. 8), 2.5 mg. daily; (Fig. 9), 5.0 mg. daily.

The magnitude of the daily fluctuation (measured as the span between the lowest and highest values) was 12 μg. during the control periods; during the administration of estrogens it increased to 27 μg. After withdrawal of medication the excretion of HPG returned to the levels observed during the pre-medication period.

Conjugated estrogens in an oral dosage of 2.5 mg. daily were given on two occasions for nine and eight days respectively.

During the first trial, HPG excretion values became negative on the sixth day of estrogen administration. Thirteen days after the withdrawal of medication, the pattern of HPG excretion was somewhat lower than during the pre-medication control period.

During the second trial, HPG excretion values were definitely reduced on the sixth day of estrogen administration, and remained at this low level for four days after withdrawal of medication. Twelve days after cessation of therapy, HPG excretion had returned to the pre-medication control levels.

TABLE 2. EFFECT OF METHYLTESTOSTERONE ON URINARY GONADOTROPIN (HPG) IN A POSTMENOPAUSAL WOMAN (DAILY ASSAYS)

Material administered	Daily dose (mg.)	No. of days	Mean HPG excretion (μg. estrone equiv./ 24 hrs.) (range)	P*	P**
None		4	5.69 (0.0 –10.60)		
Methyltestosterone	5	9	6.24 (0.0 –14.18)	>0.02<0.05	>0.1 <0.5
None		11	4.29 (0.0 –15.47)		
None		7	8.66 (0.0 –16.90)		
Methyltestosterone	25	10	12.23 (5.44–25.23)	>0.1 <0.5	>0.02<0.05
None		7	7.36 (2.90–15.12)		
None		6	6.17 (0.0 –38.03)		
Methyltestosterone	50	11	10.11 (1.22–51.88)	>0.1 <0.5	>0.5
None		7	10.14 (3.15–18.18)		
None		7	6.92 (4.56–12.81)		
Methyltestosterone	100	10	9.78 (3.84–23.29)	>0.05<0.1	>0.5
None		7	9.26 (3.66–27.32)		

* P: Significance of difference of mean value against pre-medication control.
** P: Significance of difference of mean value against post-medication control.

Table 3 shows the mean excretion values corresponding to the control periods and the periods of administration of 0.25 and 2.5 mg. of conjugated estrogens daily.

The elevated mean HPG levels observed during the last seven days of the administration of 0.25 mg. of conjugated estrogens daily differed

TABLE 3. EFFECT OF ESTROGENS ON URINARY GONADOTROPIN (HPG) IN A POSTMENOPAUSAL WOMAN (DAILY ASSAYS)

Material administered	Daily dose (mg.)	No. of days	Mean HPG excretion (μg. estrone equiv./ 24 hrs.) (range)	P*	P**
None		8	6.83 (3.49–14.23)		
		First 3	4.93†	>0.1<0.5	>0.5
Conjugated estrogens	0.25	Last 7	19.51 (3.57–36.44)	>0.01	>0.01
None		9	6.65 (1.99–13.85)		
None		9	6.86 (0.0 –32.0)		
		First 5			
Conjugated estrogens	2.5	Last 4	0.0 (0.0 – 0.0)	>0.01	>0.01
None		5	3.84 (1.27–11.74)		
None		6	5.15 (2.68– 8.78)		
					(a) >0.1<0.5
Conjugated estrogens	2.5	8	2.24†		(b) >0.1<0.05
		First 4(a)	1.11‡		
None		Last 10(b)	5.18 (1.63–22.75)		

* P: Significance of difference of mean value against pre-medication control.
** P: Significance of difference of mean control value against post-medication control.
† Results of 2 assays positive at one dose level.
‡ One-point assays.

significantly from the means for the pre- and post-medication control periods.

On one occasion, conjugated estrogens in a dosage of 2.5 mg. daily suppressed HPG excretion, and on a second occasion depressed it to a level which was maintained for four days after cessation of medication.

During the oral administration of 5.0 mg. of conjugated estrogens daily for ten days, a reduction in HPG excretion occurred on the ninth day of administration and was maintained for eight days after withdrawal of medication.

During the oral administration of 2.5 mg. daily of estrone sulfate for ten days, no effect on HPG excretion levels was observed.

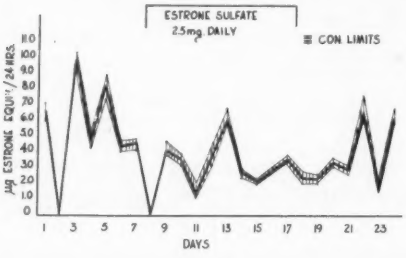

FIG. 10. Daily consecutive assays of urinary HPG in a 56-year-old normal postmenopausal woman before, during and after treatment with 2.5 mg. of estrone sulfate daily.

It is noteworthy that when HPG excretion was not lowered by the administration of estrogens in the dosages and of the type used in this study, the cyclic variation in HPG excretion was always present.

Table 4 shows the mean excretion values corresponding to the control periods and the periods of administration of 5.0 mg. of conjugated estrogens or 2.5 mg. of estrone sulfate daily.

HPG excretion on the last day of the administration of 5.0 mg. of conjugated estrogens differed significantly from the pre-medication level and from the level during the last five days of the post-medication period. Excretion was significantly lower for eight days after cessation of medication.

Mean HPG excretion during administration of estrone sulfate did not differ significantly from that during the pre- and post-medication control periods.

Norethisterone. Figures 11 and 12 show the effect on urinary HPG of the oral administration of norethisterone (17-α-ethynyl-19-nortestosterone or Norlutin) in dosages of 5, 10 and 20 mg. daily.

During the daily oral administration of 5 mg. of norethisterone, no effect on HPG excretion was noted. A cyclic variation was maintained during both control and treatment periods.

When a dose of 10 mg. of norethisterone was administered orally per

TABLE 4. EFFECT OF ESTROGENS ON URINARY GONADOTROPIN (HPG) IN A POSTMENOPAUSAL WOMAN (DAILY ASSAYS)

Material administered	Daily dose (mg.)	No. of days	Mean HPG excretion (μg. estrone equiv./ 24 hrs.) (range)	P*	P**
None		7	5.73 (0.0 –10.12)		
		First 5	8.25 (0.76–42.86)	>0.1<0.5	(a) >0.5
Conjugated estrogens	5.0				
		Last 1	1.17†	>0.01	(a) >0.01
		First 2	1.17†		
		Next 3	1.43 (1.13– 1.80)		
None		Next 3	0.44†		
		Last 5(a)	7.40 (1.03–38.03)		
None		7	5.43 (0.0 –10.32)		
Estrone sulfate	2.5	10	3.10 (0.0 – 6.71)	>0.1<0.5	>0.5
None		7	3.71 (1.62– 7.51)		

* P: Significance of difference of mean value against pre-medication control.
** P: Significance of difference of mean value against post-medication control.
† One-point assays.

day, there was no significant change in the cyclic HPG excretion compared to the pre-medication period.

When the dosage of norethisterone was raised to 20 mg. daily, HPG excretion was reduced on the fifth day of administration, and remained at a low level for three days after cessation of medication. Withdrawal bleeding occurred on the fourth post-medication control day, and lasted for three days. Six days after withdrawal of medication, HPG excretion had returned to the levels observed in the pre-medication period.

Table 5 shows the mean HPG excretion values corresponding to the control periods, and the periods of administration of 5, 10 or 20 mg. of norethisterone (Norlutin) daily.

Mean HPG excretion levels during the administration of norethisterone

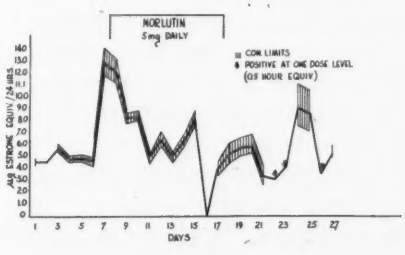

FIGURE 11

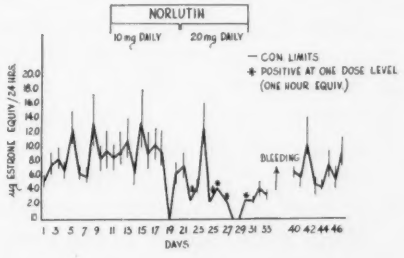

FIGURE 12

FIGS. 11 and 12. Daily consecutive assays of urinary HPG in a 56-year-old normal postmenopausal woman before, during and after oral administration of norethisterone (Norlutin) in the following dosages: (Fig. 11), 5 mg. daily; (Fig. 12), 10 mg. and 20 mg. daily.

TABLE 5. EFFECT OF 17α-ETHYNYL-19-NORTESTOSTERONE (NORLUTIN) ON URINARY GONADOTROPIN (HPG) IN A POSTMENOPAUSAL WOMAN (DAILY ASSAYS)

Material administered	Daily dose (mg.)	No. of days	Mean HPG excretion (μg. estrone equiv./ 24 hrs.) (range)	P*	P**
None		7	6.04 (4.33–14.13)		
		First 5	8.05 (4.59–13.27)	>0.1<0.5	>0.1<0.5
Norlutin	5				
		Last 5	4.70 (0.0 – 8.90)	>0.5	>0.5
None		10	5.46 (2.52–11.08)		
None		10	8.50 (5.06–17.60)		
Norlutin	10	10	8.48 (0.0 –18.22)	>0.5	(A) >0.01<0.02 (B) >0.1<0.5
		First 4	7.06†	>0.5	(A) >0.02<0.05 (B) >0.5
Norlutin	20				
		Last 6	2.04‡	>0.01	(A) >0.5 (B) >0.01
		First 3 (A)	3.41 (2.13– 5.33)		
None		Next 3			
		Last 6 (B)	6.83 (3.49–14.23)		

* P: Significance of difference of mean value against pre-medication control.
** P: Significance of difference of mean value against post-medication control.
† Result of 1 assay positive at one dose level (1 hr. equivalent).
‡ Results of 3 assays positive at one dose level (1 hr. equivalent).

in dosages of 5 and 10 mg. daily did not differ significantly from the mean levels in the pre- or post-medication periods.

Mean HPG excretion during the last six days of administration of 20 mg. of norethisterone, and for three days after withdrawal of medication, differed significantly, however, from that in the pre-medication period and during the last six days of the post-medication period.

COMMENTS

When estimating the effect of steroids on human pituitary function in postmenopausal subjects, it should be borne in mind that HPG excretion in such women is cyclic (2–4). It then follows that if HPG assays are conducted as spot tests before, during and after the administration of any given steroid, the actual effect may be masked because of the possibility of conducting the spot testing on days when HPG excretion is low or on days when, in any given cycle, the peak excretion occurs.

Most of the studies in the literature concerning the effects of methyltestosterone, estrogens and norethisterone were not conducted in postmenopausal subjects by means of the daily consecutive assay technique; therefore they will not be mentioned here.

Our data indicate that methyltestosterone in the dosages tested, did not alter HPG excretion significantly.

Albert (3), using the daily assay technique, reported the effect of the administration of 25 mg. of methyltestosterone daily in 2 subjects. In the first, a castrated woman with biliary cirrhosis, methyltestosterone did not alter HPG excretion significantly; in the second, a postmenopausal woman, HPG excretion was suppressed.

In the present study, the oral administration of conjugated estrogens caused an increase in HPG excretion within five days, when a dosage of 0.25 mg. daily was used. These data are in accordance with those of Albert and associates (3–5), who showed that a small daily dose of estrogen (0.1 mg. of stilbestrol) increased the excretion of HPG.

In our studies, the oral administration of 2.5 mg. of conjugated estrogens daily on one occasion completely suppressed HPG excretion; on a second occasion, the same dosage inhibited but did not abolish HPG excretion. In a dosage of 5.0 mg. daily, conjugated estrogens diminished HPG excretion on the last day of administration. Estrone sulfate, in a daily dosage of 2.5 mg., did not alter HPG excretion significantly.

Smith and Albert (5) found stilbestrol to be more effective than conjugated estrogens (Premarin) in comparable dosages (0.1 mg. *vs.* 1 and 10 mg. per day) in diminishing HPG excretion; abolition occurred only with 10 mg. of stilbestrol daily.

The apparent stimulating effect on HPG excretion of small doses of estrogens in postmenopausal subjects and the difference in response when methyltestosterone is administered to different subjects or when estrogens are given to the same subject on two different occasions, is of interest and warrants further investigation.

In the present study, norethisterone diminished HPG excretion when given in a daily dose of 20 mg. It has been suggested (6) that this lowering effect is due to the general properties of the 19-nortestosterones and may result either from direct action or from the weak estrogenic activity of norethisterone, as demonstrated in animal tests. The latter explanation is not in accordance with the present data, which indicate that small doses of estrogens increase rather than inhibit HPG excretion, unless there is considerable conversion of norethisterone to estrogens.

It should be noted that the present studies were conducted using the mouse uterine weight as the end-point for HPG response. This type of assay is considered to be a measure of total urinary gonadotropins; therefore no conclusions can be drawn as to the effect of the tested steroids on the individual components of the total urinary gonadotropins.

Acknowledgments

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URINARY 17-KETOSTEROIDS IN THE SYNDROME OF POLYCYSTIC OVARIES AND HYPERTHECOSIS*

ANDRÉ LANTHIER, M.D.†

The Endocrinology Laboratory and the Medical Service, Notre Dame Hospital, Montreal, Canada

ABSTRACT

The urinary 17-ketosteroid pattern was studied in 27 patients with polycystic ovaries and hyperthecosis (Stein-Leventhal syndrome). After dioxane-HCl hydrolysis of the steroids from a butanol extract of urine, the 17-ketosteroids were separated by column chromatography on silica gel, into three groups: androsterone+etiocholanolone (A+E); dehydroepiandrosterone; and the 11-oxy 17-ketosteroids. The mean value for total 17-ketosteroids was higher in the patients with the Stein-Leventhal syndrome than in normal women ($P < 0.01$), most of the difference being due to an increase in the A+E fraction ($P < 0.05$). A study was made of the behavior of the three urinary 17-ketosteroid fractions during stimulation with ACTH, suppression with 9α-fluorohydrocortisone, stimulation with HCG, estrogen therapy, and at intervals after bilateral wedge resection of the ovaries. The results permit no conclusions regarding adrenocortical versus ovarian origin of this increased secretion of urinary A+E precursor.

IN MOST medical text books the chapter on polycystic ovaries and hyperthecosis describes the condition under three subdivisions: *a*) the classic Stein-Leventhal syndrome, in which the ovaries are greatly enlarged in association with oligo-hypomenorrhea, periods of amenorrhea, infertility and hirsutism; *b*) a syndrome of hyperthecosis in which the ovaries are of normal size or only slightly enlarged in association with the classic clinical picture; and *c*) a syndrome of hyperthecosis in which the ovaries are slightly enlarged in association with meno-metrorrhagia, infertility and hirsutism. In a recent review of this subject (1) we pointed out that these three subdivisions are probably three different aspects of the same syndrome, for the following reasons: *a*) the salient clinical features are the same; *b*) the histologic pictures are almost identical; *c*) the mean urinary ketosteroid excretion is high; and *d*) all of these patients respond to bilateral ovarian wedge resection with normal menstrual periods.

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† F.R.C.P. (c).

Experimental evidence suggests that the most likely pathogenetic factor is increased secretion of androgenic steroids from either the ovary or the adrenal cortex. The present paper represents an attempt to elucidate the pathogenesis of this syndrome. The urinary 17-ketosteroid (17-KS) excretion patterns in normal women and in women with polycystic ovaries and hyperthecosis were compared during a control period, during stimulation of the adrenals with corticotropin (ACTH), during suppression of pituitary-adrenocortical activity, during administration of human chorionic gonadotropin, during estrogen therapy, and at various intervals after bilateral wedge resection of the ovaries.

MATERIAL AND METHODS

Subjects. Twenty-seven patients aged 20–35 years with the syndrome of polycystic ovaries and hyperthecosis were studied. In all the diagnosis was confirmed by histologic study of specimens obtained at the time of bilateral ovarian wedge resection. The clinical, pathologic and preliminary biochemical findings in 18 of these patients were presented and discussed in a previous paper (1).

Twelve normal young women aged 20–30 years and 8 normal young men aged 23–34 years were used as control subjects.

Hydrolysis and extraction of the urinary 17-ketosteroids. All 24-hour urine collections were stored in the frozen state until processed. A 20-ml. aliquot of urine was extracted with butanol, and a 15-ml. aliquot of the butanol extract evaporated to dryness. To the dry residue, 10 ml. of 1:4 dioxane and 1 ml. of concentrated HCl were added, and the mixture placed in a boiling water bath for ten minutes. The solution was then cooled and later evaporated to dryness in a hot-water bath (approximately 80° C.). The dry residue was dissolved in 5 ml. of absolute ethanol and 10 ml. of distilled water. Extraction was carried out with 15 ml. of ethylene dichloride. The aqueous layer was discarded and the ethylene dichloride washed with 0.1*N* NaOH. A 10-ml. aliquot was evaporated to dryness and used for chromatography.

Chromatography. A silica-gel column and two elutions were used to separate the 11-desoxy 17-KS from the 11-oxy 17-KS. Dry silica gel, purified and activated as described by Sweat (2), was placed up to a height of 11 cm. in a chromatography column having an internal diameter 0.5 mm. The dry 17-ketosteroid standards and urinary extracts were dissolved in 10 ml. of benzene and transferred to the column. Each test tube was washed with another 10 ml. of benzene which was also transferred to the column. One column was used as a blank, and another one to check the separation and recovery with appropriate 17-ketosteroid standards. When the benzene had run down completely, the first eluent (A), consisting of 85 ml. of a 1.7 per cent ethanol-benzene solution, was poured into the column and the rate of flow was adjusted to 10 drops per minute. The second eluent (B), consisted of 100 ml. of methanol. Eluate A contained the 11-desoxy 17-KS and eluate B contained the 11-oxy 17-KS. Eluates A and B were then evaporated to dryness. Recovery experiments using individual 17-ketosteroid standards, alone or added to urine, yielded values of 93.2 ± 4.2 per cent. Completeness of separation of the 11-desoxy from the 11-oxy 17-KS was checked by paper chromatography of eluates A and B, using 17-KS standards alone or added to urine.

Colorimetry. Appropriate aliquots of eluates A and B were used to measure the total

17-ketosteroid content, using the method of Drekter *et al.* (3) with the added chloroform extraction of the Zimmermann chromogens recommended by Cahen and Salter (4). Another aliquot of eluate A was used to determine the dehydroepiandrosterone content by means of the Pettenkofer reaction.

In eluate A, the total Zimmermann chromogens represent the 11-desoxy 17-KS; in eluate B they represent the 11-oxy 17-KS. The difference between Zimmermann and Pettenkofer chromogens in eluate A represents androsterone+etiocholanolone. Thus three fractions are obtained: fraction 1 is androsterone+etiocholanolone (A+E); fraction 2 is dehydroepiandrosterone (DHA); and fraction 3 contains the 11-oxy 17-KS (11-oxy).

RESULTS

Control period

In the control period, analyses of urine for the three 17-ketosteroid fractions were made as follows: 51 determinations in the 27 patients with polycystic ovaries and hyperthecosis, 21 determinations in the 12 normal young women, and 15 determinations in the 8 normal young men. The results are shown in Figure 1. The mean 24-hour total 17-KS excretion in the patients with polycystic ovaries and hyperthecosis was 3.7 mg. higher than in the normal women and 2.2 mg. lower than in the normal men. The difference was due chiefly to an increase in the A+E fraction, with smaller increases in the DHA and 11-oxy fractions. The calculated P values (Table 1) show that the total 17-KS excretion in the patients with polycystic ovaries and hyperthecosis (Stein-Leventhal syndrome) was significantly higher than in normal women ($P < 0.01$) and that probably the increase was limited to the A+E fraction ($P < 0.05$).

Stimulation: with ACTH

After two control days, urine was collected for two consecutive days during stimulation with ACTH. A 40-I.U. dose of ACTH (Acton X)[1] was administered intravenously in 500 ml. of 5 per cent glucose for a period of eight hours starting between 8 and 9 a.m. on two consecutive days. Seven patients with polycystic ovaries and hyperthecosis and 6 normal young women were studied in this manner. The values for 17-KS excretion on the second day of ACTH stimulation are shown in Figure 2. It is apparent that the 24-hour excretion of total 17-KS on the second day of ACTH stimulation was 7.7 mg. higher in the patients with the ovarian syndrome than in the normal young women, and that this difference was due mainly to an increase in the A+E fraction (5.2 mg.), with a smaller increase in the DHA fraction (3.2 mg.).

[1] Acton X, utilized for the ACTH tests, was kindly supplied by Nordic Biochemicals, Montreal; and A.P.L. (Human Chorionic Gonadotrophin) by Ayerst, McKenna & Harrison Ltd., Montreal, Canada.

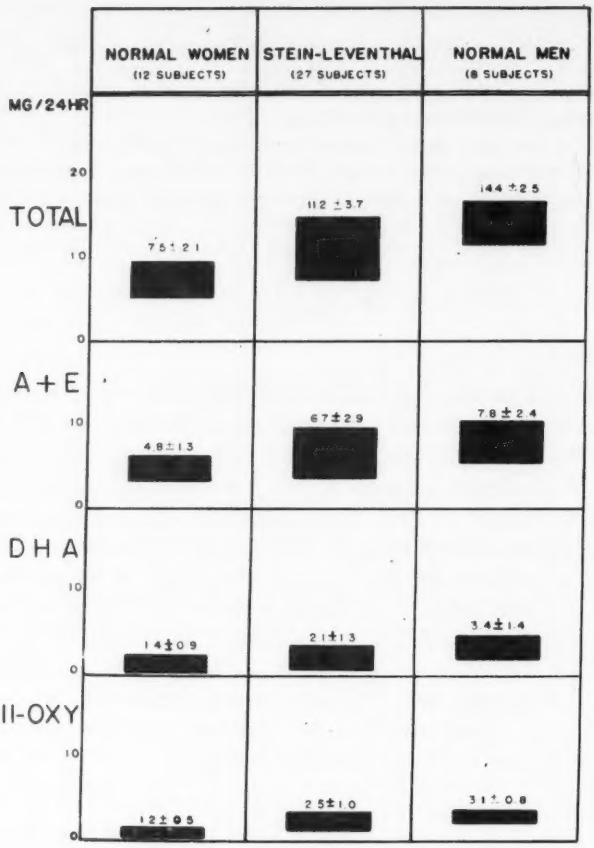

FIG. 1. Urinary excretion of 17-ketosteroids during control period. The values above each block are the mean and standard deviation.

TABLE 1. COMPARISON OF CALCULATED P VALUES FOR THE THREE URINARY 17-KETOSTEROID FRACTIONS IN WOMEN WITH POLYCYSTIC OVARIES AND HYPERTHECOSIS (STEIN-LEVENTHAL SYNDROME), NORMAL WOMEN, AND NORMAL MEN

Subjects	P values			
	Total 17-KS	A+E	DHA	11-Oxy
Normal men *vs.* Normal women	<0.001	<0.01	<0.01	<0.001
S-L syndrome *vs.* Normal women	<0.01	<0.05	<0.1	<0.7
S-L syndrome *vs.* Normal men	<0.05	<0.4	<0.05	<0.2

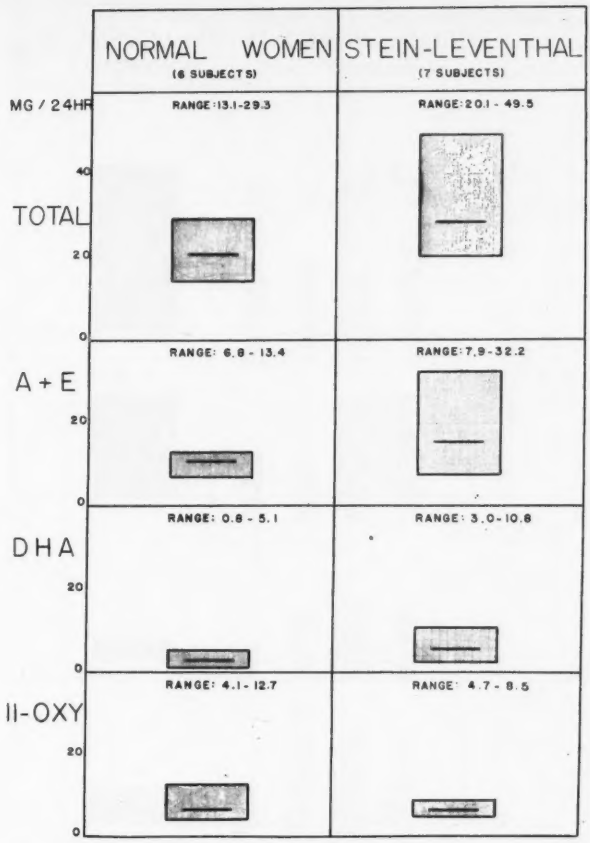

FIG. 2. Urinary excretion of 17-ketosteroids on day 2 of stimulation with ACTH intravenously. Mean values are indicated by the horizontal line inside each block.

Pituitary-adrenocortical suppression

After two days of control urine collections, pituitary-adrenocortical suppression was produced with 9α-fluorohydrocortisone (5 mg. per day for three days) in 3 patients with polycystic ovaries and hyperthecosis and in 3 normal young women. The results obtained on the third day of suppression are shown in Figure 3. All three urinary 17-KS fractions were suppressed to equally low levels in both groups of subjects.

Stimulation with human chorionic gonadotropin (HCG)

After two to four days of control urine collections, human chorionic gonadotropin (A.P.L.)[1] was given in a dosage of 5,000 I.U. per day intra-

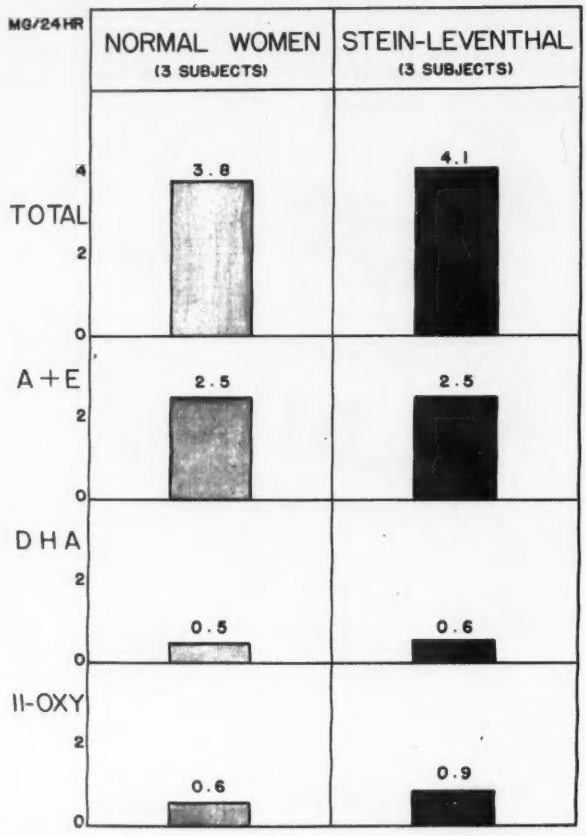

FIG. 3. Urinary excretion of 17-ketosteroids on day 3 of pituitary-adrenocortical suppression with 9α-fluorohydrocortisone. Mean values are noted above each block.

muscularly for four days, followed by three more days of control urine collections. This procedure was carried out in 4 patients with polycystic ovaries and hyperthecosis, in 1 normal woman and in 2 ovariectomized women. No effect was noted on any of the three urinary 17-KS fractions in the ovariectomized women. The effects on the A+E fraction in the other subjects are shown in Figure 4. In the normal woman used as a control, HCG produced an increase in the urinary excretion of A+E which was still noticeable two days after stopping administration. In 3 of the patients with the ovarian syndrome the increase in the excretion of A+E during administration of HCG was approximately of the same magnitude as that in the normal woman; but in the fourth patient no effect was demonstrated. No

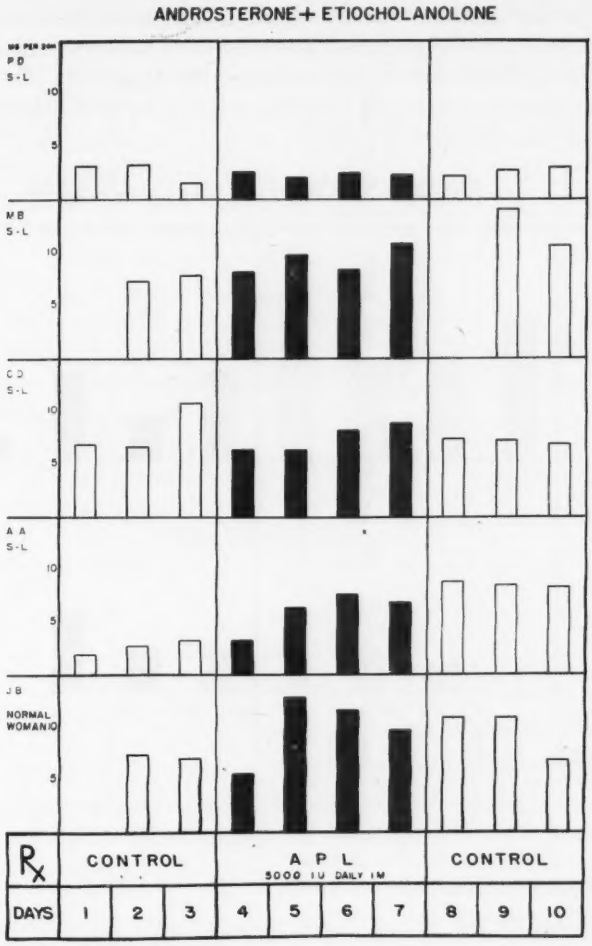

FIG. 4. Urinary excretion of A+E fraction before, during and after administration of human chorionic gonadotropin in 1 normal woman (last row) and in 4 women with polycystic ovaries and hyperthecosis (S-L syndrome).

significant alterations in urinary DHA and 11-oxy fractions were noted in any of the subjects studied during stimulation with HCG.

Estrogen administration

After a control period of three or four days, ethynyl-estradiol (0.2 mg. per day for four days) was given by mouth to 2 patients with polycystic ovaries and hyperthecosis. The effects on the urinary A+E fraction are shown in

Figure 5. In one patient the excretion of A+E decreased markedly, whereas in the other patient it was not modified. There was no significant alteration in the DHA and 11-oxy values in either patient. The results in these 2 cases were too equivocal to justify a larger series, so this part of the investigation was not pursued further.

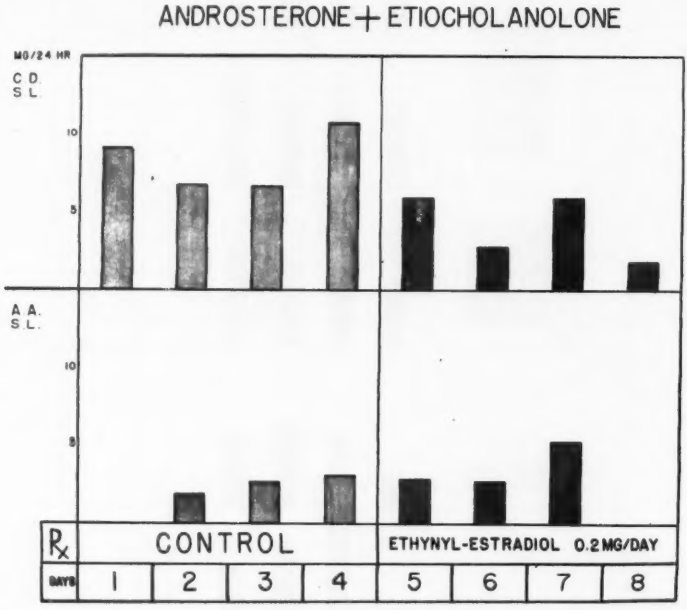

FIG. 5. Urinary excretion of A+E fraction before and during administration of ethynylestradiol in 2 women with polycystic ovaries and hyperthecosis (S-L syndrome).

Bilateral wedge resection of the ovaries

Fractionation of the urinary 17-ketosteroids at various intervals after bilateral wedge resection of the ovaries was performed in 11 patients with polycystic ovaries and hyperthecosis who had been studied preoperatively. One patient with hirsutism but normal menstrual periods and 1 normal woman, both of whom had undergone a bilateral wedge resection of the ovaries during a laparotomy for other reasons, were also studied. The effects of resection on the urinary excretion of A+E in all these patients are shown in Figure 6. There was no significant modification of the DHA and 11-oxy values in any of the subjects. In the normal woman (J.T.), the A+E value was unchanged three months after the resection. In the patient with hirsutism and normal menstrual periods (P.D.), the A+E value was unchanged sixteen months after operation. Three types of response to bi-

lateral ovarian wedge resection were observed in the patients with polycystic ovaries and hyperthecosis. In 3 (L.E., S.D. and C.D.) there was a marked decrease in the excretion of A+E, which persisted even twelve months later in one of them (S.D.). In Patient M.R., there was a pronounced fall in the excretion of A+E one week after resection, but three and twelve months later the level was even higher than before operation. In the other 7 cases there was no significant change in the A+E value up to six months after resection. It should be noted that all these patients responded to bilateral ovarian wedge resection with normal menstrual cycles.

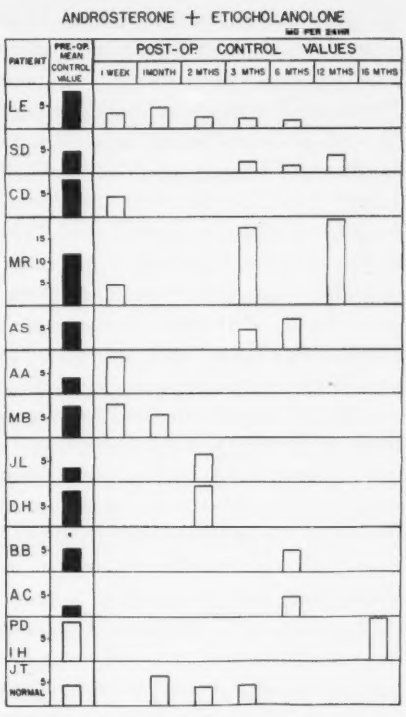

FIG. 6. Urinary excretion of A+E fraction before and at various intervals after bilateral wedge resection of the ovaries in 11 women with the Stein-Leventhal syndrome, in 1 woman with idiopathic hirsutism (P.D.), and in 1 normal woman (J.T.)

DISCUSSION

Since the original description by Stein and Leventhal (5) in 1935 of this syndrome consisting of menstrual irregularities, infertility and hirsutism with large polymicrocystic ovaries and hyperthecosis, there has been much speculation regarding its etiology and pathogenesis. The most logical theory seems to have been that of an increased androgenic steroid production by either the ovaries or the adrenal cortex. Early attempts to establish a correlation between hirsutism and the total urinary 17-ketosteroids in this disease were generally unsuccessful (6–8). More recently, the urinary 17-ketosteroids have been studied after fractionation by various column and paper chromatographic techniques utilizing different hydrolytic procedures. Although it is difficult to compare these studies with one another and with our own study because of differences in methodology, a certain trend is apparent, especially in the more recent data obtained in larger series of cases.

We have reviewed a number of the better documented series from the literature for comparison with our own results. A completely normal chro-

matographic pattern of urinary 17-ketosteroids has been reported in a total of 18 cases of the Stein-Leventhal syndrome by Jailer and Vande Wiele (6), Buxton and Vande Wiele (7), Gemzell, Tillinger and Westman (8) and Pesonen, Timonen and Mikkonen (9). A slightly increased excretion of the 11-oxy 17-ketosteroids has been described in a total of 15 patients by Pesonen, Timonen and Mikkonen (9), Gallagher *et al.* (10) and Lipsett and Riter (11). An elevated excretion of dehydroepiandrosterone has been found in 5 cases by Perloff *et al.* (12). The most constant finding, especially in the more recent studies, has been that of an increased urinary excretion of androsterone and etiocholanolone. This has been reported in a total of 35 patients by Pesonen, Timonen and Mikkonen (9), Gallagher *et al.* (10), Lipsett and Riter (11), Hermann, Buchner and Morris (13), Johnsen (14) and Netter *et al.* (15).

Our own results in the 27 cases shown in Figure 1 demonstrate that the mean values for the total urinary 17-ketosteroids and for the three fractions fall approximately half-way between those for normal women and those for normal men. Statistical analysis demonstrates that the mean value for A+E in the patients with polycystic ovaries and hyperthecosis is significantly higher than that in normal women ($P<0.05$) but is not significantly lower than that for A+E in normal men ($P<0.3$).

The data on the 64 cases from the literature and the statistical analysis of our own 27 cases apparently justify the conclusion that in the syndrome of polycystic ovaries and hyperthecosis, the mean value for total urinary 17-ketosteroids is higher than the mean value in normal women, and that most of the difference can be accounted for by an increased excretion of A+E. This finding seems to support the assumption that in the syndrome of polycystic ovaries and hyperthecosis there is an increased production of an androgenic steroid which is metabolized to androsterone and etiocholanolone. In order to explore the possible adrenocortical or ovarian origin of this androgenic steroid, the behavior of the urinary 17-ketosteroid fractions and particularly the A+E fraction was studied during stimulation with ACTH, suppression with 9α-fluorohydrocortisone, stimulation with HCG, estrogen therapy, and after bilateral wedge resection of the ovaries.

Herrmann, Buckner and Morris (13) found that during stimulation with ACTH (25 I.U. intravenously for eight hours on one day) the excretion of A+E was slightly lower in 4 patients with the Stein-Leventhal syndrome than in 4 normal female control subjects. Our results in 7 cases (Fig. 2) were different and so was our method of ACTH stimulation (40 I.U. intravenously for eight hours on two consecutive days). The 24-hour total urinary 17-ketosteroids were 7.7 mg. higher than in the 8 normal female control subjects and most of the difference was due to the A+E fraction.

The effect of pituitary-adrenocortical suppression on the urinary 17-ketosteroids has been studied by many authors, including Gallagher *et al.* (10),

Perloff *et al.* (12) and Hermann, Buckner and Morris (13), using different natural or synthetic corticosteroids in various dosages. The conclusions seem to be uniform, *i.e.*, whether the control urinary 17-ketosteroid fractions were normal or elevated, they were significantly reduced during suppression therapy. Our own studies (Fig. 3) confirm these observations and do not support the report of contrary findings by Jailer and Vande Wiele (6).

The increase in excretion of the A+E fraction during stimulation with ACTH and the decrease in excretion during suppression with 9α-fluorohydrocortisone (comparable to that in normal subjects) is strongly suggestive of an adrenocortical origin of the precursor of A+E.

It is possible, nevertheless, that a small, more or less constant amount of precursor of ovarian origin could produce a similar pattern of response to stimulation and suppression. There is no doubt that the normal ovary produces androgenic steroid. Bradbury and Gaensbauer (16) in 1939 demonstrated that administration of gonadotropin could stimulate the ovaries of immature female rats to produce both estrogens and androgens. Katsh (17) in 1950 reported the androgenic activity of ovarian transplants to the seminal vesicle in castrated adult male rats. Indirect evidence of androgenic steroid production by human ovaries was published by Dingemanse and Huis in t'Veld (18) in 1951. More direct evidence was furnished by Zander (19), Solomon, Vande Wiele and Lieberman (20) and Lanthier and Sandor (21) in studies on bovine and human ovaries. The effects of administration of HCG on the urinary excretion of 17-ketosteroids have been studied by a number of workers. Because various dosage schedules and methodologic variations have been employed, the results are difficult to evaluate and compare with our own. Segaloff, Sternberg and Gaskill (22) reported that administration of HCG produces theca luteinization and hilar-cell hyperplasia of the ovaries in normal adult women. The latter finding was also reported by Sternberg, Segaloff and Gaskill (23). In the same two studies, an increase in total urinary 17-ketosteroids was also noted by Segaloff *et al.* (22) in 3 of 5 subjects and by Sternberg *et al.* (23) in 4 of 6 subjects. Plate (24) demonstrated increased urinary excretion of androsterone and etiocholanolone during administration of HCG in normal women, a finding which was also reported by Netter *et al.* (25). On the other hand, Gemzell, Diczfalusy and Tillinger (26) did not find any significant change in the total urinary 17-ketosteroids during administration of HCG in 30 women with primary or secondary amenorrhea. Three of our 4 patients with polycystic ovaries and hyperthecosis responded to HCG by an increase in the urinary excretion of A+E, a response which was not significantly different from that obtained in the normal woman used as a control subject. To eliminate the possible participation of the adrenal cortex in this response to HCG, a similar investigation was carried out in 2 ovariectomized women;

there was no change in any of the urinary 17-ketosteroid fractions. The latter results are at variance with those of some earlier reports. Hibbitt, Starnes and Hill (27) found a slight increase in the total urinary 17-ketosteroids of castrated adult men during treatment with HCG. A slight increase was also noted by Jayle *et al.* (28) in 6 castrated adult men, in whom it was also shown that this effect was due to an increase in A+E. Plate (29) reported increased excretion of all the urinary 17-ketosteroid fractions during treatment of ovariectomized women with HCG. Although it is possible that part of the increased urinary excretion of A+E during administration of HCG may be derived from adrenocortical precursors, the response observed in patients with polycystic ovaries and hyperthecosis is not significantly different from the response observed in normal women.

Administration of estrogen was used as a measure to suppress endogenous secretion of pituitary gonadotropin, and the effect on the urinary 17-ketosteroid fractions was studied. In one patient with the Stein-Leventhal syndrome no change was observed, whereas in another there was a decrease in the A+E fraction. Hermann, Schindl and Bondy (30), utilizing a higher estrogen dosage in 6 normal men and 3 normal women, reported a decrease in the urinary excretion of A+E and also a diminished response of these two steroids to ACTH.

In only a few cases of Stein-Leventhal syndrome has chromatographic separation of the urinary 17-ketosteroids been performed after bilateral wedge resection of the ovaries. Pesonen, Timonen and Mikkonen (9) observed a decreased level of androsterone and etiocholanolone in 8 cases, whereas Hermann, Buchner and Morris (13) noted a decreased level of androsterone only, and no change in etiocholanolone thirty days postoperatively in 4 cases. The steroid values in our cases were not constant, but all of the patients responded with normal menstrual periods to bilateral wedge resection of the ovaries. In 3 patients there was a decrease in the excretion of A+E, which was still apparent twelve months postoperatively. In another case there was a temporary decrease of A+E, but three months later, the level was even higher than before operation. In the other 7 patients, as in the normal woman and in the patient with hirsutism and normal menstrual periods, there was no significant change in any of the urinary 17-ketosteroid fractions up to six months postoperatively.

Our findings demonstrate that in the syndrome of polycystic ovaries and hyperthecosis, there is a significant increase in the urinary excretion of A+E.

The results of stimulation with ACTH and of suppression with 9α-fluorohydrocortisone, although suggestive, do not permit the conclusion that in this syndrone there is an excessive adrenocortical secretion of a precursor of A+E, as proposed by Gallagher *et al.* (10). It is still possible that a small,

fairly constant, ovarian overproduction of a precursor of A+E may induce the same urinary pattern of response. On the other hand, the results of stimulation with HCG and the administration of estrogen do not permit the conclusion that the ovary is the source of hypersecretion of a precursor of A+E in the Stein-Leventhal syndrome. The almost universal clinical success of bilateral wedge resection of the ovaries is difficult to reconcile with the variation in the response of the urinary 17-ketosteroid fractions. One is tempted to theorize that when there is a lasting postoperative decrease in urinary A+E, ovarian wedge resection has blocked excessive ovarian secretion of a precursor of A+E. In cases in which lack of a postoperative decrease in A+E suggests an adrenocortical origin of the precursor, there seems to be no experimental basis for making this finding fit into a logical scheme. Although it appears simple to affirm that in the patients responding to exogenous steroid therapy there must be an important adrenocortical component in the pathogenesis of the Stein-Leventhal syndrome, we do not feel justified in accepting this conclusion without further experimental evidence.

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A DIAGNOSTIC RADIOIODINE UPTAKE TEST IN PATIENTS RECEIVING ANTITHYROID DRUGS*

I. D. THOMAS, M.B., B.S., T. H. ODDIE, D.Sc. AND J. MYHILL, M.Sc.†

Unit of Clinical Investigation, Royal North Shore Hospital of Sydney, Crows Nest, N.S.W., Australia

ABSTRACT

In 74 patients uninfluenced by thyroid-affecting medication, the fraction of an intravenously injected tracer dose of I^{131} present in the thyroid region ten minutes after injection (N_{5-15}) was calculated and plotted against the one-hour uptake rate. The curve thus obtained was used as a calibration curve in subsequent studies. Forty-one patients were studied under two or more of the following regimens: (i) untreated; (ii) receiving a full course of antithyroid drug treatment; (iii) receiving a thyroid hormone preparation in "suppressive" dosage; (iv) receiving a combination of (ii) and (iii). Multiplying the ten-minute thyroidal I^{131} uptake rate in a patient receiving antithyroid drugs by a factor of 1.22 yields the basic untreated one-hour uptake rate. The ten-minute uptake rate is suppressible by a thyroid hormone preparation in nonthyrotoxic patients but is not suppressible in thyrotoxic patients.

INTRODUCTION

MOST tests used clinically for the determination of thyroid function by measurement of the radioiodine uptake rate are temporarily invalidated by the prior administration of an antithyroid drug. It is necessary to discontinue the administration of the drug long enough before the test for the blocking effect to be dissipated, and sometimes a thyroid hormone preparation must be given for from one to three weeks to distinguish thyrotoxic high uptake from nonthyrotoxic high uptake (1, 2). During this period of cessation of antithyroid drug therapy, severe clinical manifestations may develop in some thyrotoxic patients. Even when such an untoward development does not occur, the delay in instituting definitive treatment may be inconvenient for both the patient and the physician.

An accurate diagnostic method which does not require the discontinuance of existing therapy would be of practical value.

Several methods (3–7) of estimating thyroid function by following the early stage of iodine uptake have been described. Higgins (8) used the

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measurement of the thyroidal uptake of I^{131} ten minutes after intravenous injection of a tracer dose. He showed that the phase of thyroidal iodine metabolism being observed was that of the inorganic iodine "trap," the evidence for this being that the rate of iodine accumulation during this early period was not appreciably altered by the prior administration of carbimazole, but was greatly inhibited by potassium perchlorate. Similar studies (unpublished) had also been proceeding in this Unit; the iodine uptake rates were expressed in the same terms[1] as those used in a one-hour uptake method previously described (9).

The present studies are based on the observation that the very early uptake rate is little affected by thyroid-blocking agents, and show that a clear distinction between thyrotoxic and nonthyrotoxic patients can be made without discontinuing the antithyroid treatment which may already have been instituted.

CLINICAL MATERIAL AND METHODS

Patients

Studies were made on 115 patients referred for diagnosis or treatment.

The assessment of thyroid function of each patient was made by a review of all available data, including clinical evaluation, response to treatment, estimation of serum protein-bound iodine concentration, and measurement of the thyroidal radioiodine uptake rate. Patients who had received recent therapy with a substance known to affect the entry of inorganic iodine into the thyroid gland (for example, iodides or potassium perchlorate) were not included in the study.

Methods

Forty-one of the 115 patients were studied while influenced by thyroid-affecting medication in one or more of the following ways:

(i) after elapse of one week since receiving any thyroid-affecting medicine;

(ii) after having received an antithyroid drug in full dosage (carbimazole, 10 mg., or propylthiouracil, 100 mg., every eight hours) for at least three full days before the test, the last dose having been given within three hours of beginning a radioiodine uptake test;

(iii) after having received a thyroid hormone preparation (thyroxine, 0.3 to 0.5 mg. per day for from fourteen to twenty-eight days, or triiodothyronine, 120 to 150 μg. per day for from three to seven days), the last dose having been administered within three hours of beginning a radioiodine uptake test;

(iv) after having received a combination of an antithyroid drug as described in (ii) and a thyroid hormone preparation as described in (iii).

Uptake rates were observed following the intravenous injection of a tracer dose of approximately 10 μc. of I^{131}. The method used for the calculation of the uptake rate at one hour was that of Oddie *et al.* (9). An additional counting period was observed in all patients from the fifth through the fifteenth minute after injection of the tracer dose. During this period, counts of radioactivity were made over the neck for two minutes out of every three. These neck counts, corrected for background and distance and expressed

[1] The thyroidal uptake rate is expressed as k_1, the fraction of the inorganic iodide compartment cleared per minute by the thyroid gland.

as a fraction of the injected dose, were plotted on graph paper, the ordinate being the neck uptake (N) and the abscissa being the time of the count. From the smooth curve through the plotted points was derived the mean ten-minute neck uptake (N_{5-15}).

For 74 cases uninfluenced by medication, N_{5-15} was plotted against the radioiodine uptake rate $1G^3k_1$ calculated in the usual manner from one-hour uptake readings (Fig. 1). The curve thus obtained was used as a calibration curve, so that in subsequent studies, when N_{5-15} had been derived, the uptake rate at the time of observation (ten-minute uptake rate) was read directly from the graph.

RESULTS

Untreated patients

For the 74 patients unaffected by antithyroid drugs, agreement between the ten-minute uptake rate and the one-hour uptake rate was tested by calculating the logarithm, x, of their ratio, where

$$x = \log_{10} \frac{k_1 \text{ from one-hour reading}}{k_1 \text{ from ten-minute reading and calibration curve}}.$$

The mean value of x was $+0.0001$, with a standard deviation of individual values of 0.0935.

Thus, at the 5 per cent level of probability, $x = 0.183$, corresponding to a ratio of 1.52 for the one-hour uptake versus the ten-minute uptake. At the 1 per cent level, $x = 0.241$, corresponding to a ratio of 1.74. At the 0.1 per cent level, $x = 0.308$, corresponding to a ratio of 2.03. The factor by which a ten-minute reading derived in this way is likely to differ from the corresponding one-hour uptake is therefore not inconsiderable, even at the 5 per cent level.

Treated patients

The results in the 41 patients (21 euthyroid and 20 hyperthyroid) who received medication are summarized in Table 1.

In this table the values listed in column B are those obtained in a standard one-hour uptake test when the patient was not receiving thyroid-affecting drugs ("basic uptake").

The tabulated results have been subdivided according to the functional diagnosis—hyperthyroid or euthyroid—but from the standpoint of comparison of ten-minute uptake rates with basic uptake rates, no difference existed between thyrotoxic and euthyroid subjects.

Comparison of the data in column A of Table 1 with those in column B shows that measurements of the ten-minute uptake rate are sufficiently in accord with the basic rate for the same diagnostic criteria (10) to be applied.

The values in column D are clearly much lower than the corresponding basic uptake rates, reflecting the degree of "blocking" of organic binding of iodine. When the one-hour uptake in a patient receiving antithyroid drugs

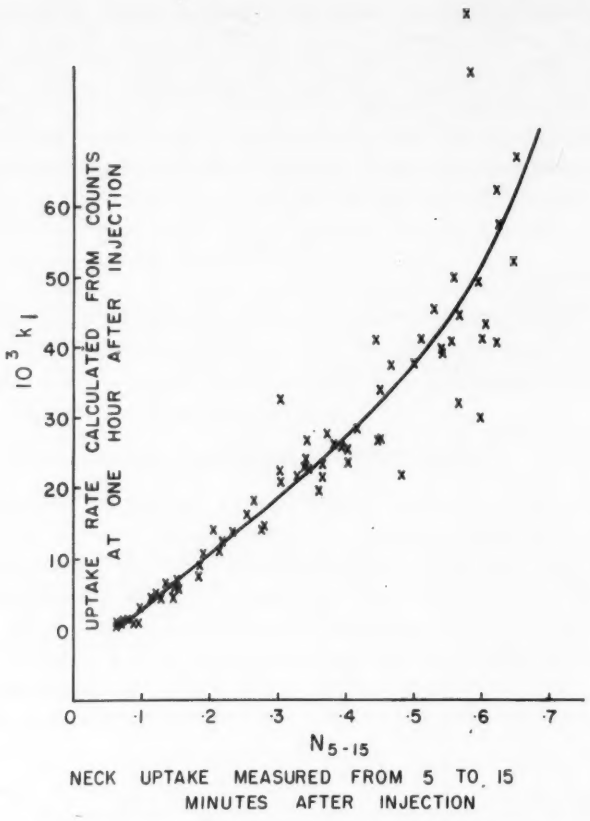

FIG. 1. Calibration curve for fifteen-minute thyroidal I^{131} uptake rates.

is not much lower than the basic uptake, it is reasonable to conclude that the therapy is not achieving its desired objective.

Column C corresponds much better with column B than does column D, but the blocking effect of the antithyroid drug is already evident.

In 20 patients, the ten-minute uptake while receiving an antithyroid drug and the basic (untreated) one-hour uptake were calculated.

Using for this group

$$x = \log_{10} \frac{k_1 \text{ of basic uptake}}{k_1 \text{ of ten-minute uptake with antithyroid drug}}$$

it was found that the mean value of x was $+0.0965$, corresponding to a ratio of 1.22.

The standard deviation of individual values of x was 0.0977, and the standard error of the mean was 0.0218.

TABLE 1. TEN-MINUTE AND ONE-HOUR UPTAKE RATES IN 21 EUTHYROID AND 20 HYPERTHYROID PATIENTS DURING DIFFERENT REGIMENS OF MEDICATION

Diagnosis	Case No.	Thyroidal I^{131} uptake rate (k_1)*							
		No treatment		During treatment with antithyroid drug		During treatment with thyroid hormone prep.		During treatment with thyroid prep. +antithyroid drug	
		A** 10-min.	B 1-hr.	C 10-min.	D 1-hr.	E 10-min.	F 1-hr.	G 10-min.	H 1-hr.
Euthyroid	1	37	22			9.9	9.7		
	2	57	41			6.5	6.3		
	3	32	27			9.4	7.4		
	4	16	18			2.3	3.3		
	5	7.7	6.9	6.6	7.3		4.4	5.3	4.7
	6			17.8	10.9	4.2	2.4		
	7	17	14.2	11.6	9.1	4.9	4.6	2.0	3.0
	8		7.6	5.2	2.4				
	9	4.4	4.4			0.4	0.6		
	10	4.5	5.1	4.3		2.8	3.2		
	11	25	22	26	20				
	12	11.5	9.2			7.3	4.6		
	13	51	36			1.9	1.6		
	14	5.7	8.8			2.0	1.0		
	15		7.2	8.0	5.4				
	16	5.5	6.7			0.7	1.6		
	17			40	17			1.9	1.7
	18			7.2	4.1			0	0.2
	19		13.3	13.8					
	20	24	16	13.5					
	21	37	42					2.0	0.8
Hyperthyroid	22	28	26	22	13				
	23	10	10.8	7.1	3.5	12.3	12.4		
	24			65	38	45	42		
	25	34	38	30	24	32	41		
	26	49	80			45	50		
	27			47	18	44	34		
	28	59	49	41	16	65	55		
	29	48	88	32	18				
	30	51	50	30	36	47	45		
	31	22	27	21	12.7	27	26		
	32	36	44			29	27		
	33	21	25			21	23		
	34	24	24	25	14.7				
	35		28	16.8	5.0				
	36	21	22	20	8.9				
	37		5.7	4.0					
	38	28	26	22					
	39	39	41			35	32		
	40			57	20			22	7.5
	41	33	33			35	33		

* See footnote 1 in the text.
** Letters are for identification of columns.

At the 5 per cent level of probability $x = 0.288$, corresponding to a ratio of 1.94 for the one-hour uptake versus the ten-minute uptake. At the 1 per cent level, $x = 0.348$, corresponding to a ratio of 2.23. The factor by which the ten-minute reading is likely to differ from the corresponding one-hour uptake is again not small, even at the 5 per cent level.

Nevertheless, the mean value of x differs significantly from zero. Therefore, while the patient is affected by an antithyroid drug, it is necessary to multiply the derived ten-minute uptake rate by a factor of 1.22 to deduce the basic untreated uptake rate.

Comparison of columns E and F with columns A and B shows that both the ten-minute uptake and the one-hour uptake are suppressible by a thyroid hormone preparation in euthyroid subjects. Equally evident is the non-suppressibility in hyperthyroid subjects.

Illustrative case

Case 7. The patient was a 33-year-old male. An unequivocal diagnosis of thyrotoxicosis had been made elsewhere twelve months previously. At that time he manifested irritability, loss of weight, a hyperkinetic circulatory state, lid lag, and goiter. The diagnosis had been confirmed with radioiodine uptake studies and estimation of the serum protein-bound iodine level. Since then he had been receiving continuous treatment with propylthiouracil, 100 to 150 mg. daily in divided dosage.

When first seen in this Clinic he was symptom-free and had no clinical signs of thyrotoxicosis; the thyroid gland was not palpably enlarged. He was taking 150 mg. of propylthiouracil daily. The serum protein-bound iodine concentration was 6.5 μg. per 100 ml. The thyroidal ten-minute I^{131} uptake rate was 11.6 (uncorrected), or 14.2 (corrected by application of the factor of 1.22), and the one-hour uptake rate was 9.1.

During the ensuing seven days, propylthiouracil was continued in the same dosage, and triiodothyronine was given (150 μg. in fractional doses daily). With this therapy, the one-hour uptake rate was 2.98 and the ten-minute uptake rate was 2.0 (uncorrected) or 2.4 (corrected). This degree of suppression indicated (2) that the gland was not thyrotoxic and that antithyroid therapy need not be continued.

Table 1 shows other confirmatory results obtained in this patient during different regimens of medication. He has subsequently been followed for six months without therapy, and there is no evidence of recurrence of thyroid overactivity.

DISCUSSION

Measurement of the ten-minute thyroidal radioiodine uptake by the method described yields results expressed in the terms used in the one-hour uptake method, which now has well-defined diagnostic criteria (10) for two population groups and which serves as the basis of a system of radioiodine dosage in the treatment of thyrotoxicosis (11). The ten-minute method is no more technically difficult than the one-hour method, the practicality of which is illustrated by its use in the performance of over 3,000 tests in the period from April 1957 to March 1960 in this Unit.

The advantage of the ten-minute method for the patient in whom treatment has already been commenced lies in these factors: 1) that the antithyroid treatment need not be interrupted while the diagnosis is being made; 2) that the method reveals the underlying functional state of the thyroid gland as distinct from the level of thyroid hormone production, which may be lowered as the result of successful treatment; 3) that com-

pensatory hyperplasia of the thyroid due to overtreatment may be distinguished just as well by a suppression test with this method as with others; and 4) that when performed in conjunction with the one-hour uptake measurement, it is a guide to the completion of "blocking" achieved by the antithyroid regimen.

The test is not applicable when a drug (such as iodide or perchlorate) has been administered which interferes with the entry of inorganic iodide into the thyroid gland. When counts of radioactivity are low, the statistical accuracy of neck counts made at a short interval after injection of the tracer may be impaired; therefore the test is not applicable in hypothyroid patients.

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KARYOTYPIC ANALYSIS OF A MALE PSEUDOHERMAPHRODITE WITH THE SYNDROME OF FEMINIZING TESTES*

ERNEST H. Y. CHU, PH.D., MELVIN M. GRUMBACH, M.D.† AND AKIRA MORISHIMA, M.D.‡

Biology Division, Oak Ridge National Laboratory§, Oak Ridge, Tennessee; and the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, and Babies Hospital, New York, N. Y.

ABSTRACT

A case of clinically diagnosed male pseudohermaphrodism with the syndrome of feminizing testes in a 26-month-old child, is presented. Chromosome analysis of tissue biopsy specimens by *in vitro* culture techniques demonstrated a diploid chromosome number of 46, including an X and a Y chromosome. This finding, in agreement with the findings in other reports, refutes the theory that an XXY sex chromosomal constitution accounts for the clinical manifestations of this syndrome. The hypotheses of genetic controls by a sex-linked recessive or a sex-limited autosomal dominant gene have been considered, but the existing genetic evidence is too inadequate to distinguish between the two possibilities.

AMONG the heterogeneous group of disorders that have been classified as male pseudohermaphrodism, a common well-defined group is associated with the syndrome of feminizing testes (1–3). The complete form of this syndrome is characterized by female external genitalia, primary amenorrhea, absent or scanty axillary and pubic hair, and the development of breasts and a female habitus at puberty. The vagina terminates in a blind pouch. In most instances, a vas deferens and epididymis are present bilaterally; the testes may be situated intra-abdominally, in the inguinal region, or in herniae within the labia majora. The nuclear chromatin pattern is of the male type.

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‡ Fellow in Pediatric Endocrinology, College of Physicians and Surgeons, Columbia University, New York.

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The hereditary nature of male pseudohermaphrodism with feminizing testes is suggested by the high familial incidence. It is transmitted through the maternal line and affects only males (4). A recent analysis of 16 affected pedigrees supports the contention that this disorder is transmitted by either a sex-linked recessive or a sex-limited dominant mutant gene (2). The apparent excess of affected males over normal males within families, although not statistically significant (2), has been used as evidence to support an alternative hypothesis; Petterson and Bonnier (4), Taillard and Prader (5), and Danon and Sachs (6) suggested a chromosome anomaly in which affected individuals were postulated to have an XXY sex chromosome constitution. Danon and Sachs found, in skin biopsy specimens from 2 cases, fewer chromocenters per cell than in normal females but more than in normal males, and an increased number of nuclei with 3 chromocenters. They interpreted this finding as consistent with an XXY chromosome constitution. However, the latter interpretation has been questioned (2). The fact that in Klinefelter's syndrome the cells have XXY sex chromosomes (7–9) argues strongly against this hypothesis. When Barr's method for interpreting the sex chromatin pattern in various tissues was used, a male chromatin nuclear pattern was consistently observed. Furthermore, in 1942 Severinghaus (10) reported an XY constitution in the spermatocytes of a male pseudohermaphrodite with the incomplete form of this syndrome.

Recent advances in tissue culture and cytologic techniques have made possible the direct and more critical delineation of human chromosomes. Chu and Giles (11) made chromosome determinations in a male pseudohermaphrodite, using thyroid biopsy material grown *in vitro*, and showed that this individual had 46 chromosomes, including an X and a Y chromosome. In the present communication the karyotype of a male pseudohermaphrodite with the syndrome of feminizing testes is reported.

CASE REPORT

A 26-month-old female infant was admitted to Babies Hospital in May 1959 for investigation of bilateral masses in the labia majora. The 19-year-old mother had had a son and a daughter by other fathers. The circumstances did not permit us to examine the female sibling. There was no history of sterility or primary amenorrhea in the antecedents. The mother had a normal amount of pubic and axillary hair; menarche occurred at age 12 years, and her menstrual history was unremarkable. The significant findings on examination of the patient were limited to the external genitalia (Fig. 1). The labia majora were soft and fleshy; each labium contained a smooth, firm, ovoid mass that measured about 1.5 cm.×1.0 cm. and was consistent with a prepuberal testis. The clitoris was not enlarged. Separate vaginal and urethral orifices were identified, and the introitus had a normal appearance. A uterus was not felt on rectal examination.

The nuclear chromatin pattern in smears of the buccal mucosa and a skin biopsy specimen was of the male type. The excretion of urinary 17-ketosteroids was 0.3 to 0.5 mg. per twenty-four hours. No abnormalities were detected by intravenous pyelography.

FIG. 1. The external genitalia of a 26-month-old male pseudohermaphrodite with the syndrome of feminizing testes. Bilateral masses in the labia majora are clearly visible.

The concentration of serum nonprotein nitrogen was 33 mg. per 100 ml. A vaginogram showed a vaginal pouch, but a cervix and uterine canal were not detected.

Both inguinal regions were explored surgically. Testes of normal size, and an epididymis and vas deferens were identified bilaterally. No Müllerian elements were detected. Biopsy specimens of each testis, vas deferens and epididymis were obtained for histologic examination and for cell culture. The microscopic appearance of the testis is shown in Figure 2.

RESULTS AND DISCUSSION

The general procedure of primary cell culture by means of trypsinization and cytologic preparation for chromosome analyses has been described previously (11). In the present case, most cells examined were derived from cultures of the left epididymis. Of 44 cells analyzed in detail, 41 cells had 46 chromosomes including one X and one Y chromosome. One cell had 43 chromosomes and 2 others had 44 chromosomes. A departure of this kind from the count in the majority of cells is probably caused by artifacts. Three additional cells derived from cultures of an inguinal lymph node, and 1 cell from the right epididymis had also 46 (including X and Y) chromosomes. The chromosome complement of 1 cell from the culture of the left epididymis, arranged in pairs, is presented in Figure 3.

Recently Jacobs *et al.* (12) reported that, in 4 instances, individuals with the syndrome of feminizing testes had a normal diploid number of chromosomes and an XY chromosome sex. An additional instance of the same chromosome constitution has been reported by Puck *et al.* (13). The XY sex-chromosome constitution is consistent with the male-type sex chromatin pattern found in patients with this syndrome.

The present observations, together with those of Jacobs *et al.* and Puck *et al.* and an earlier case (11), furnish additional evidence in support of the suggestion by Grumbach and Barr (2) that this syndrome is transmitted by either a sex-linked recessive or a sex-limited dominant mutant gene. Pedi-

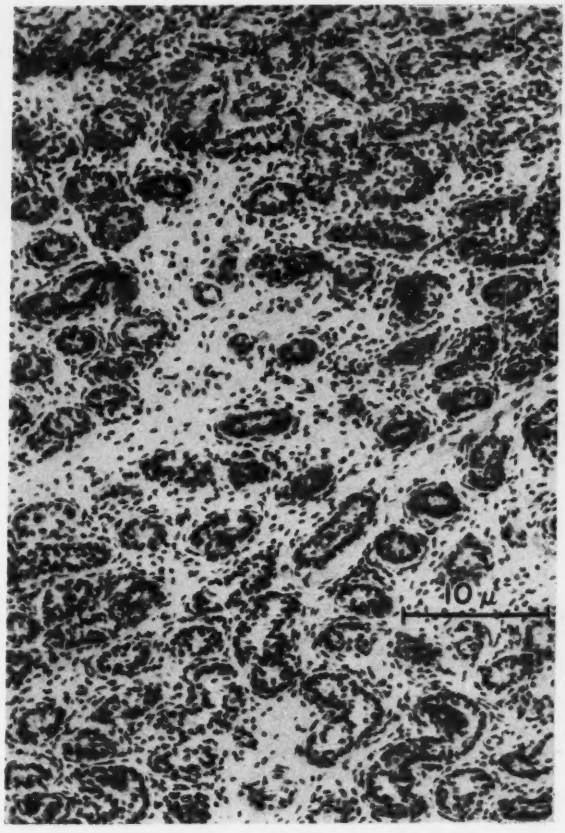

FIG. 2. Histologic section of the right testis showing immature seminiferous tubules, an adequate number of spermatogonia, a small amount of granular material within the lumen of some tubules, and the absence of Leydig cells. (H and E stain.)

grees have been described in which a sex-linked recessive trait such as color blindness (14) or hemophilia (15) occurred coincidently with the syndrome of feminizing testes. On the basis of these pedigrees, Puck *et al.* (13) stated that the inheritance of this syndrome as a sex-limited dominant is highly probable, since the involved gene is not closely linked to either of the other two sex-linked recessives. If the linkage group corresponding to the human X chromosome was known to be a short one, such a conclusion would be more plausible. In the absence of information concerning the genetic length of the X chromosome, however, the possibility must be retained that the length is great enough to accommodate three sex-linked mutants in such a manner that one mutant need not be closely linked to

either of the other two. Furthermore, a perusal of the known linkage maps available for the mouse (16) indicates that mammalian linkage groups can certainly be long enough to accommodate three such genetic loci. It would seem reasonable to conclude, therefore, that the published pedigrees do not as yet furnish enough genetic evidence to enable us to discriminate between the two alternative modes of inheritance. Such a conclusion would not discourage collection of data that could reveal a loose but discernible linkage

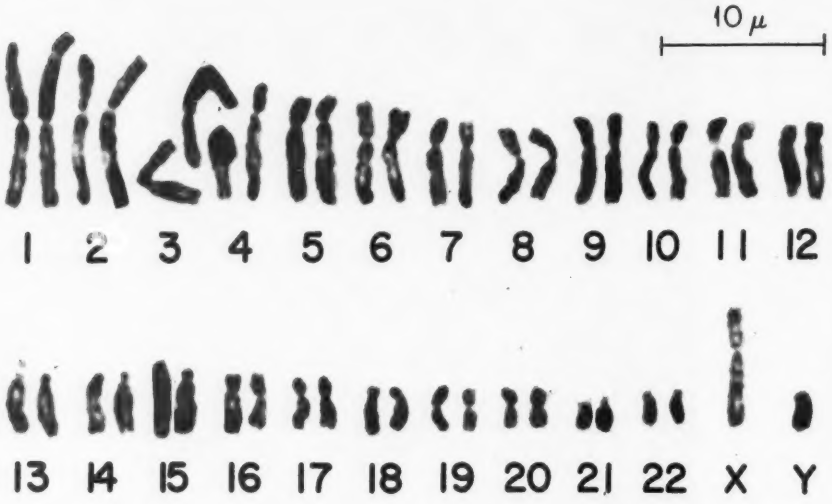

FIG. 3. The karyotype of a cell grown in a culture derived from a biopsy specimen of the left epididymis, showing 22 pairs of autosomes and the X and Y chromosomes. (Aceto orcein stain.)

between sex-linked traits and the mutant that accounts for the syndrome of feminizing testes if the latter trait is in fact located on the X chromosome.

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POLYURIA AFTER OPERATION FOR TUMORS IN THE REGION OF THE HYPOPHYSIS AND HYPOTHALAMUS

RAYMOND V. RANDALL, M.D., EDWARD C. CLARK, M.D., HENRY W. DODGE, JR., M.D. AND J. GRAFTON LOVE, M.D.

Sections of Medicine, Neurology, and Neurologic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

ABSTRACT

Four patterns of change in the daily urinary volumes were observed in 43 patients in whom polyuria developed subsequent to operation for tumors in the region of the hypophysis and hypothalamus. 1) Brief polyuria developed in 12 patients and was followed by a permanent return of the urinary volumes to normal levels. 2) Transient polyuria was followed in 15 patients by normal urinary volumes (interphase) and later by permanent polyuria. 3) Permanent polyuria developed without an interphase in 10 patients. 4) A variation of the second pattern was seen in 6 patients in whom there was an initial peak of increased urinary output followed by a partial return toward normal, and finally permanent polyuria. Although the basis for the various urinary patterns of polyuria could not be determined, it is assumed that the surgical procedures induced changes in the hypothalamico-neurohypophyseal system comparable to those which are known to cause similar patterns of polyuria in experimental animals.

ALTHOUGH it is well known that polyuria[1] may occur in human beings after surgical procedures in the region of the hypophysis and hypothalamus, few detailed observations of urinary volumes during the onset of this condition have been published. Dandy (1), in 1940, noted the onset of polyuria in a 17-year-old girl after the hypophyseal stalk had been divided during an exploratory craniotomy. More recently Ikkos and co-workers (2) and Lipsett and co-workers (3) recorded their experiences with polyuria in patients after hypophysectomy for the treatment of metastatic cancer. In 1957, we reported the onset of polyuria in 3 patients after operation for tumors in the region of the hypophysis and hypothalamus (4, 5). Thomas (6), in 1957, mentioned that this syndrome was observed in 4 of 9 patients operated on for tumors in this region.

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[1] The term "polyuria" is used in this paper in preference to "diabetes insipidus" because it is not established that the basis for the polyuria observed in patients immediately after surgical procedures in the region of the hypophysis and hypothalamus is actually a deficiency of antidiuretic hormone.

Studies on experimental animals (7–13) indicate that at least three patterns of change in urinary volume characterize the development of polyuria after damage to the hypothalamico-neurohypophyseal system: 1) Temporary polyuria, which may last several days. Subsequently, some impairment of urinary concentration may persist but a normal urinary volume is usually maintained. 2) The classic triphasic pattern which consists of transient polyuria, a period of essentially normal urinary output called the "interphase," and then permanent polyuria. 3) Immediate and permanent polyuria, which develops without an interphase.

This report will describe the course of polyuria in 43 patients during the first few days after operation for tumors in the region of the pituitary and hypothalamus. The report is limited to a description of observed phenomena, since elucidation of the anatomic and physiologic factors in the production of polyuria in patients who undergo intracranial surgery of this type is not feasible at the present time.

MATERIAL AND METHODS

The 43 patients included in this study were operated on at the Mayo Clinic between 1953 and 1960 for tumors in the region of the pituitary and hypothalamus. Omitted from the study are 23 additional patients in whom polyuria developed subsequent to intracranial operation but who were given antidiuretic hormone before the pattern of urinary excretion was evident. Also omitted are patients who had diabetes insipidus prior to surgical intervention.

The tumors harbored by the 43 patients included chromophobe adenoma of the pituitary in 25, craniopharyngioma in 10, eosinophilic adenoma of the pituitary in 2, chordoma in 2, and epidermoid cyst, optic glioma, meningioma, and hemangio-endothelioma in 1 each.

In this study, urinary volumes in excess of 3000 ml. per twenty-four hours were considered to be abnormal. All patients were permitted to eat and drink as they wished. The intake of fluids and the excretion of urine were measured from midnight to midnight. In selected cases, frequent determinations of the specific gravity of the urine were made. The use of antidiuretic hormone was avoided until the urinary pattern had become evident. Our experience with these patients was similar to that of other observers in that the intake of fluid virtually paralleled the excretion of urine and the specific gravity of the urine was inversely proportional to the volume of urine. Hence, for the sake of brevity, only the data on urinary volumes are presented in this report.

Each patient received 200 mg. of cortisone acetate intramuscularly for at least two days before operation and on the morning of operation. After operation, the daily intramuscular dose of cortisone was progressively reduced for several days. Thereafter the administration of cortisone was either discontinued or continued in dosages of 25 to 30 mg. orally each day. On the day of operation, most patients received intravenously 500 to 2000 ml. of 5 per cent dextrose in water, physiologic salt solution, or 5 per cent dextrose in physiologic salt solution. Some also received 500 to 1500 ml. of such fluids intravenously on the day after operation and occasionally on the second and third days after operation.

OBSERVATIONS

After operation, the changes in urinary excretion fell into one of four patterns.

Pattern 1. Twelve patients had brief, transient polyuria (Fig. 1) that began one to four days after operation, lasted one to six days, and was followed by a return of normal urinary volumes (Table 1). No further polyuria is known to have developed in these patients. The maximal daily volume of urine occurred one to seven days after operation and varied between 3460 and 13,425 ml.

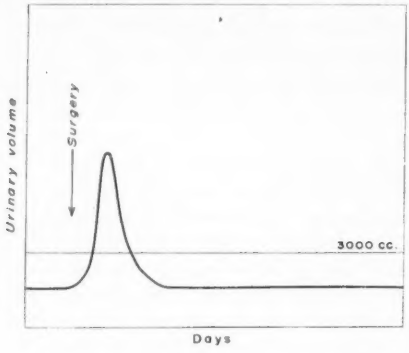

FIG. 1. Schematic curve showing pattern 1—temporary diabetes insipidus.

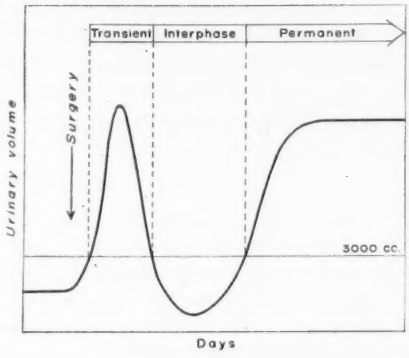

FIG. 2. Schematic curve showing pattern 2—triphasic pattern of diabetes insipidus.

Pattern 2. Ten patients had a classic triphasic pattern (Fig. 2) while under observation in the hospital (Table 2, Cases 13 to 22 inclusive). The transient phase of polyuria began within two days after operation and lasted one to five days. The maximal daily volume of urine occurred between the first and third days after operation and varied from 3625 to 27,930 ml. The transient phase of polyuria was followed by a period of essentially normal urinary output (interphase) which lasted one to five days. During the interphase, the daily urinary volume in each case was less than 2000 ml., and in all but 3 cases the volume fell to less than 1000 ml. at one point. Polyuria returned between the fourth and ninth days after operation and the maximal output varied between 5250 and 14,740 ml. per twenty-four hours. The latter values may not represent the largest possible volumes, because in most instances the use of antidiuretic hormone was begun at this time since the urinary pattern had been defined.

An additional 5 patients (Table 2, Cases 23 to 27 inclusive) had transient polyuria followed by an interphase which was observed for three to nine

TABLE 1. PATTERN 1: TRANSIENT POLYURIA

Case	Age (yrs.) & sex	Type of tumor	Polyuria			
			Onset (days after operation)	Maximal volume		Duration (days)
				Days after operation	Urine (ml./24 hrs.)	
1	59 F	Chromophobe	1	2	3460	2
2	55 F	Chromophobe	1	1	4025	1
3	46 M	Chromophobe	2	7	4200	6
4	39 M	Craniopharyngioma	2	2	4215	1
5	58 M	Chromophobe	1	1	4400	1
6	13 M	Chordoma	1	1	4450	1
7	43 F	Chromophobe	1	1	4925	2
8	56 M	Chromophobe	2	1	5300	3
9	49 M	Chromophobe	4	6	5675	5
10	38 M	Optic glioma	1	1	6640	1
11	29 M	Chromophobe	1	1	7250	3
12	15 F	Hemangio-endothelioma	1	1	13,425	5

days before they left the hospital. There was no information about the exact day the interphase ended and the polyuria returned, but in each instance polyuria returned within a few days after the patient left the hospital. These cases are of practical importance because, as emphasized by Clark and associates (4), the interphase may be mistaken for a permanent return of normal urinary volume unless the patient is observed for an adequate time.

Pattern 3. Permanent polyuria (Fig. 3) developed in 10 patients without

TABLE 2. PATTERN 2: TRIPHASIC PATTERN OF POLYURIA

Case	Age (yrs.) & sex	Type of tumor	Polyuria, transient phase				Interphase, duration in days	Polyuria, permanent phase		
			Onset (days after after operation)	Duration (days)	Maximal volume			Onset (days after operation)	Maximal volume	
					Days after operation	Urine (ml./24 hrs.)			Days after operation	Urine (ml./24 hrs.)
13	37 F	Craniopharyngioma	0*	2	1	3625	2	4	6	8175
14	57 M	Chromophobe	2	2	3	4050	3	7	14	7700
15	46 F	Chromophobe	1	2	2	4200	2	5	5	8252
16	55 M	Chromophobe	1	2	2	4650	5	8	9	5250
17	37 M	Chromophobe	2	2	2	7125	3	7	10	9250
18	37 M	Eosinophilic	1	1	1	7250	3	5	5	7095
19	50 F	Chromophobe	1	5	1	7450	1	7	9	7070
20	44 M	Craniopharyngioma	0	4	1	11,625	5	9	12	11,050
21	17 M	Craniopharyngioma†	0	4	1	11,720	2	6	7	12,225
22	9 M	Chordoma‡	0	4	1	27,930	3	7	9	14,740
							Interphase, days observed			
23	44 F	Meningioma	3	2	3	3800	6	In each case permanent polyuria began after the patient left the hospital.		
24	7 M	Craniopharyngioma	3	2	3	4125	5			
25	49 M	Chromophobe	1	1	1	5475	9			
26	45 M	Chromophobe	1	5	2	6300	3			
27	36 M	Chromophobe	0	3	1	11,800	5			

* 0=Day of operation.
† Case reported previously by Randall and associates (5).
‡ Case reported previously by Clark and associates (4).

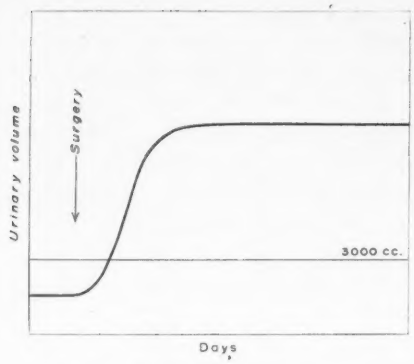

FIG. 3. Schematic curve showing pattern 3—immediate and permanent diabetes insipidus.

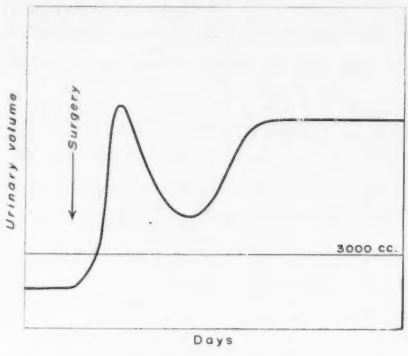

FIG. 4. Schematic curve showing pattern 4—a variation of pattern 2.

an intervening interphase (Table 3). Polyuria began between the day of operation and four days thereafter. The maximal urinary volume occurred one to seven days after the surgical procedure and ranged from 5175 to 11,760 ml. per twenty-four hours. These volumes may not be maximal because some of the patients were given antidiuretic hormone after the urinary pattern had been defined.

Pattern 4. Six patients (Table 4) had a urinary pattern (Fig. 4) which was a variation of pattern 2. In each case, polyuria began within six days after operation. The maximal daily volume came on the same day or the day after polyuria began and varied between 4400 and 13,220 ml. The daily urinary volume then decreased but never returned to a normal level.

TABLE 3. PATTERN 3: IMMEDIATE AND PERMANENT POLYURIA

Case	Age (yrs.) & sex	Type of tumor	Polyuria		
			Onset (days after operation)	Maximal volume	
				Days after operation	Urine (ml./24 hrs.)
28	59 F	Chromophobe	2	7	5175
29	57 M	Chromophobe	0*	2	6880
30	45 M	Epidermoid cyst	1	1	7000
31	51 M	Chromophobe	1	1	7750
32	55 M	Chromophobe	1	1	7975
33	11 F	Craniopharyngioma	1	2	9050
34	34 M	Craniopharyngioma	1	1	9200
35	18 F	Craniopharyngioma	1	2	9550
36	20 F	Craniopharyngioma	4	6	11,400
37	55 M	Chromophobe	0	1	11,760

* 0 = Day of operation.

TABLE 4. VARIATION OF PATTERN 2

Case	Age (yrs.) & sex	Type of tumor	Polyuria			Minimal volume		Polyuria, second peak	
			Onset (days after operation)	First peak		Days after operation	Volume of urine (ml./24 hrs.)	Days after operation	Volume of urine (ml./24 hrs.)
				Days after operation	Volume of urine (ml./24 hrs.)				
38	65 F	Chromophobe	6	6	4400	8	2850	10	4425
39	43 M	Craniopharyngioma	1	1	6675	4	4100	7	6800
40	30 F	Chromophobe	2	2	7175	4	3850	8	8200
41	20 F	Eosinophilic	1	1	9220	5	3150	8	6000
42	36 F	Chromophobe	1	2	9600	5	6025	6	9250
43	41 M	Chromophobe	1	1	13,220	4	7100	6	13,800

Finally, the urinary excretion increased, reaching a maximal value between 4425 and 13,800 ml. per twenty-four hours. The latter values may not represent the greatest possible volumes, since the patients were given antidiuretic hormone or were dismissed from the hospital before additional observations could be made.

COMMENT

Some patients had varying degrees of anterior pituitary failure prior to operation and others had normal pituitary function, but no correlation could be established between the preoperative function of the pituitary and the various patterns or intensity of polyuria. There was also no correlation between the type of tumor and the patterns of polyuria. The interval of time between operation and the onset of polyuria was not related to the type or amount of solutions administered intravenously to the patients. Likewise, the patients with the largest volumes of urine were not necessarily those who received the largest amounts of saline solution.

Although Robson and Lambie (14) reported that cortisone was thought to have induced polyuria in 2 patients after hypophysectomy, it seems unlikely that cortisone primarily accounted for the patterns of polyuria observed in the present study. A recent review (15) of patients operated on for chromophobe adenoma of the pituitary showed that polyuria developed postoperatively in only 14 of 50 patients, even though all 50 had received virtually the same amounts of cortisone. Not only is it difficult to ascribe the occurrence of several different patterns of polyuria to cortisone alone, but we observed similar patterns of postoperative polyuria before cortisone became available. It seems more likely that anatomic changes secondary to operation account for the patterns of polyuria seen in some patients after operation for tumors in or near the sella turcica. It is possible, however, that cortisone may potentiate other mechanisms for postoperative polyuria.

Since there were no necropsy cases among the patients in this study, we can only speculate about the possible anatomic basis for the observed patterns of polyuria. Presumably, during and following operation, changes

occurred in the hypothalamico-neurohypophyseal system comparable to those which are known to cause similar patterns of polyuria in experimental animals.

Anatomic studies have provided reasonable explanations for the several patterns of polyuria which are associated with lesions in the hypothalamico-neurohypophyseal system of experimental animals (7–12). Temporary polyuria is thought to result from transient failure of the posterior portion of the pituitary body to release antidiuretic hormone after minor injury to the hypothalamico-neurohypophyseal system. Within several days, function of the system returns, antidiuretic hormone is released, and polyuria disappears (13). This pattern has been seen either when the pituitary stalk has been injured and the posterior lobe has been left in place or when the posterior lobe of the pituitary has been removed. Presumably, in the latter instance antidiuretic hormone is secreted by the median eminence.

The triphasic pattern may be produced in experimental animals by transection of the pituitary stalk and destruction of the median eminence, provided the posterior lobe of the pituitary is left in place. It is postulated that the resulting denervation of the posterior lobe inhibits release of antidiuretic hormone, thus causing immediate polyuria. After several days, the denervated posterior lobe degenerates and discharges its store of antidiuretic hormone to cause the interphase characterized by virtually normal urinary output. When the store of antidiuretic hormone is exhausted, the interphase ends and permanent polyuria ensues (16). If the posterior lobe of the animal is removed, the stalk transected, and the median eminence destroyed, immediate and permanent polyuria develops without an interphase. Hence, the posterior lobe of the pituitary seems to be essential to the development of the interphase in experimental animals. However, the fact that the hypophysectomized patients of Ikkos and coworkers (2) had a triphasic pattern of urinary excretion suggests that the presence of a degenerating posterior lobe may not be necessary for the development of an interphase in human beings. Clarification of this point must await further study.

Despite tremendous exchanges of water in some patients, no significant alteration in the status of hydration was observed, provided patients were able to drink as they wished. We observed an extreme example of this situation in a 9-year-old boy (Table 2, Case 22) weighing 110 pounds (50 Kg.) who had a chordoma removed from the region of the optic chiasm. The day after operation his urinary excretion was 27,930 ml. per twenty-four hours and his intake of fluid was 29,820 ml., each amount being greater than half his body weight. There was no change in his state of hydration or in his serum electrolyte level during the period of observation.

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INTERSTITIAL-CELL TUMOR OF THE TESTIS: REPORT OF TWO CASES

JOHN A. WARD, M.D.*, SIMON KRANTZ, M.D.†, JOSEPH MENDELOFF, M.D.‡ AND EARL HALTIWANGER, M.D.§

Atlanta Veterans Administration Hospital and Emory University School of Medicine, Atlanta, Georgia

ABSTRACT

Two cases of interstitial-cell tumor of the testis with gynecomastia in adults are reported. In Case 1 a metastatic lesion developed in the area of the pedicle of the left kidney. Urinary 17-ketosteroid excretion increased to exceedingly high levels. Urinary estrogens were markedly increased whereas pituitary gonadotropins were undetectable at 6.6 mouse units. 17-Hydroxysteroids remained normal until four months prior to death. Hypertension developed about fifteen months prior to death, which occurred five years after removal of the original tumor and three years after the first evidence of intra-abdominal metastatic disease. Case 2 was operated on successfully and the patient is in apparent good health ten years after surgery.

INTERSTITIAL-CELL tumors of the testis are relatively rare. They comprised only 1.2 per cent of Dixon and Moore's (1) series of 990 testicular tumors. Generally these tumors are benign. However, in a recent survey of the literature, Dalgaard and Hesselberg (2) tabulated over 90 cases of interstitial-cell tumor—a group in which the incidence of malignancy was approximately 10 per cent. Because of the rarity of these interstitial-cell tumors, we wish to report 2 cases, in one of which metastases developed. In reviewing 104 cases of testicular tumors treated at the Atlanta VA Hospital from 1935 to 1957, only 2 cases of interstitial-cell tumor were found—an incidence of less than 2 per cent.

CASE HISTORIES

Case 1

First Admission

J. L., a 54-year-old white male aircraft worker, was first admitted to this hospital on September 29, 1950, for a nasal polypectomy, and was discharged on October 13, 1950.

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* Clinical Investigator, Atlanta VA Hospital, and Instructor in Medicine, Emory University School of Medicine.

† Chief of Radiology Service and Tumor Registry, Atlanta VA Hospital, and Associate Professor of Radiology, Emory University School of Medicine.

‡ Chief of Pathology Service, Atlanta VA Hospital, and Associate Professor of Pathology, Emory University School of Medicine.

§ Chief of Urology Service, Atlanta VA Hospital, and Instructor in Surgery, Emory University School of Medicine.

Second admission

He was in the hospital again from July 19, 1954 to August 2, 1954, for treatment of postnasal drip. He weighed 204 pounds and his blood pressure was 140/70 mm. Hg. Physical examination revealed nasal polyps and what was described as a large left hydrocele. The urologic consultant's report stated, "a medium-sized thick-walled left hydrocele which does not transilluminate well—tumor cannot be ruled out without aspiration or surgery." The right testis was atrophic. There was a history of right-sided mumps orchitis. A chest roentgenogram was interpreted as showing cardiac enlargement, most likely left ventricular. Results of routine laboratory determinations, including serologic studies, blood count and urinalysis, were within the limits of normal.

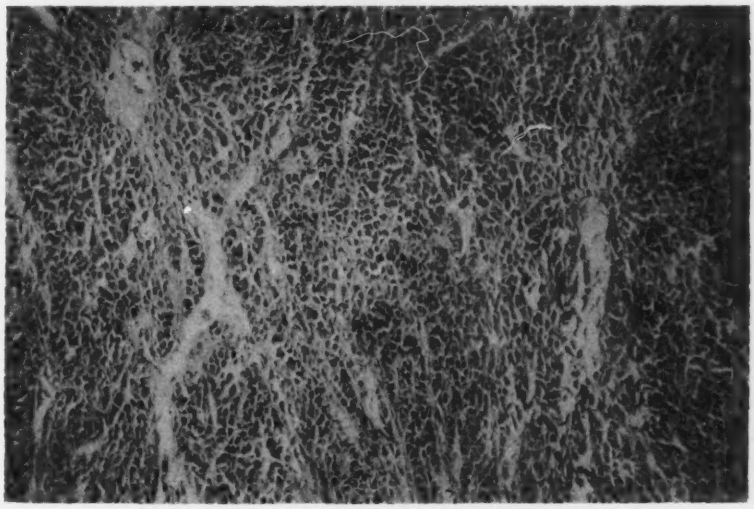

FIG. 1. *Case 1.* Organoid arrangement of uniform polygonal cells in primary testicular tumor. (Hematoxylin and eosin, reduced from 125×.)

Surgical exploration of the left scrotal contents on July 22, 1954, revealed practically no hydrocele, but a large testis. A *simple orchiectomy* was performed.

The gross pathology report was as follows: The specimen consisted of the left testis, which measured 6.0 cm. in diameter. The tunica vaginalis was thickened, measuring 7.0×8.0 cm., and contained a few scattered small greyish nodules. The testis had been replaced by firm, dark brown tissue and there was no recognizable testicular parenchyma.

Microscopic examination. There was extensive replacement of the testicular parenchyma by tumor tissue; only a few compressed seminiferous tubules remained. Most of these tubules were atrophic; however, in a few there was still some maturation of the germinal epithelium. The tumor was composed of strands and cords of medium-sized polygonal cells (Fig. 1). For the most part the cells were uniform and contained round nuclei, prominent nucleoli, and both fine and coarse chromatin (Fig. 2). The cytoplasm was eosinophilic, granular, and contained occasional vacuoles which showed a positive staining reaction for fat. There were occasional mitotic figures and rare crystalloids.

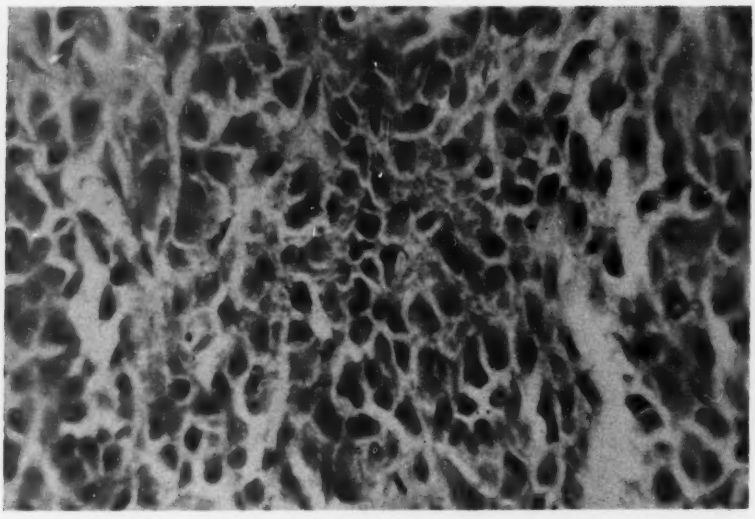

FIG. 2. *Case 1.* Uniform polygonal cells in primary testicular tumor. (Hematoxylin and eosin, 537×.)

In many places the tumor was separated from the surrounding structures by dense connective tissue. However, tumor deposits were found in the hilus. There were also several deposits of tumor cells in vascular channels of the capsule of the testis and in the epididymis (Fig. 3). There were no tumor deposits in any of the vascular channels of the cord.

An *intravenous pyelogram* made January 5, 1956, revealed hydronephrosis and lateral displacement of the lower pole of the left kidney. The ureter was not visualized. The collecting system of the right kidney and ureter were normal (Fig. 4).

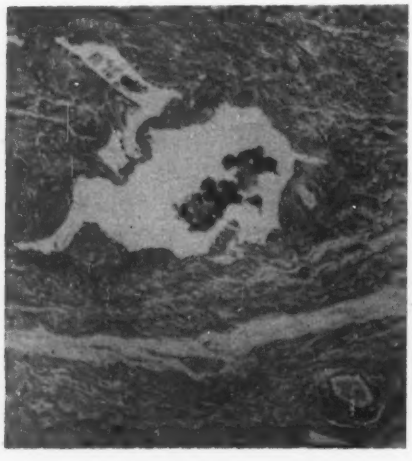

FIG. 3. *Case 1.* Cluster of tumor cells in vascular channel of capsule of testis. (Hematoxylin and eosin, 125×.)

FIG. 4. *Case 1.* Intravenous pyelogram, January 5, 1956, showing hydronephrosis and lateral displacement of the lower pole of the left kidney.

FIG. 5. *Case 1.* Retrograde pyelogram, June 18, 1956, showing lateral deviation of the left upper ureter and lower pole of left kidney.

Third admission

The patient was admitted for the third time on May 7, 1956 (discharged on July 26, 1956) for pain of ten days' duration in the left costovertebral angle radiating to the left para-umbilical region. He had noted tender gynecomastia during the preceding year. After orchiectomy there had been an initial loss of libido and potentia, but these had returned to some extent.

Physical examination showed a weight of 178 pounds, blood pressure 135/85 mm. Hg, and prominent gynecomastia with palpable plaques of hypertrophic breast tissue underlying enlarged tender areolae. The abdomen was tender to deep palpation and a tender mass was palpable in the left mid-abdomen. From May 8, 1956 to May 29, 1956 the mass was treated by x-ray therapy—a total of 3200 roentgens (measured in air) equally divided between anterior and posterior ports. Examination during and following the radiation therapy revealed no change in the size of the mass, although there was symptomatic relief from pain.

A retrograde pyelogram showed, in addition to hydronephrosis, lateral deviation of the left upper ureter and lower pole of left kidney (Fig. 5).

On July 17, 1956, surgical exploration of the abdomen revealed a hard nodular retroperitoneal tumor extending from the left renal pedicle to 1 inch above the bony pelvis. Another "golf-ball sized" metastasis was found just medial to the right kidney.

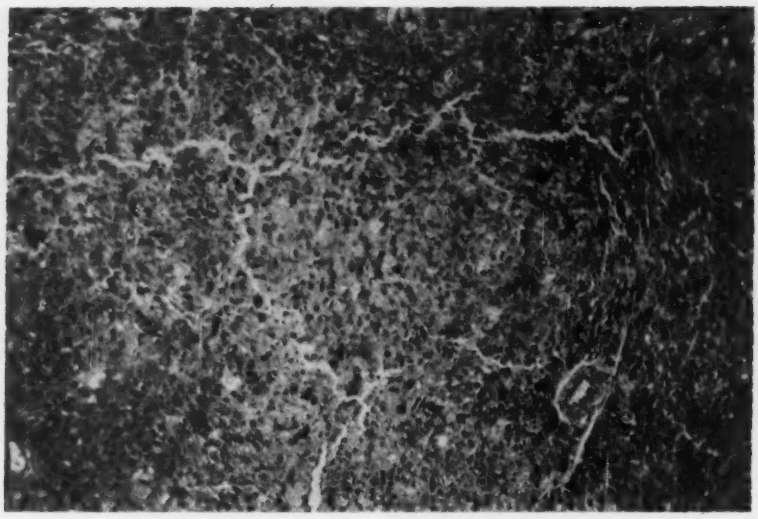

FIG. 6. *Case 1.* Metastatic lesion in perirenal soft tissue. There is loss of organoid pattern, and variation in cellular size and type. (Hematoxylin and eosin, reduced from 125×.)

Left nephrectomy was not performed because of involvement of the renal pedicle with tumor. A biopsy of the perirenal mass showed metastatic interstitial-cell carcinoma. The basic histologic pattern and general appearance were similar to those of the original testicular tumor (Fig. 6). A few cells contained crystalloids. However, there was a scattering of giant tumor cells, some of which were mononuclear and monstrous, whereas others were multinucleated. Rare cells contained hyperchromatic nuclei. Cellular atypism and anaplasia were marked in contrast to the lack of these features in the primary lesion (Fig. 7).

Fourth admission

The patient was in the hospital again from October 26, 1956 to November 19, 1956 for treatment of nasal obstruction due to polyps. Blood pressure was 142/82, and weight 184 pounds. The physical findings were otherwise unchanged, except for tenderness of the right testis.

Fifth admission

The patient was admitted again on February 17, 1958 because of left flank pain of one week's duration and passage of blood clots in the urine. Blood pressure was 150/70, and weight 187½ pounds. Previous physical findings were unchanged. From February 19, 1958 to March 7, 1958 (the day of discharge) the tumor was treated by x-irradiation in a total dosage of 3600 roentgens through two ports. This caused some relief of pain.

Outpatient department

He was seen as an outpatient on March 4, 1958 and on April 4, 1958; blood pressures were 155/90 and 220/125, respectively.

On July 14, 1958, blood pressure was 198/100. He had noted hematuria for one to

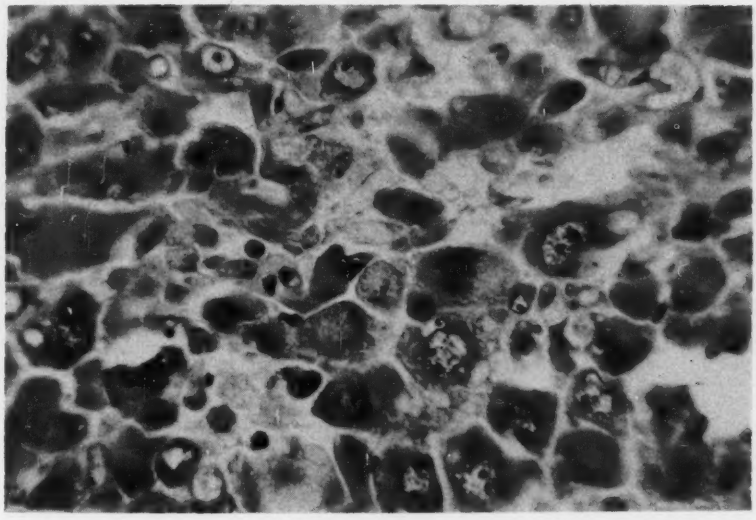

FIG. 7. *Case 1.* Metastatic lesion in perirenal soft tissue, showing markedly atypical cells. Many are enlarged, with vesicular nuclei containing multiple nucleoli. (Hematoxylin and eosin, 537×.)

two days, but he was working daily, with some limitation due to left flank pain.

On October 14, 1958, despite treatment from his private physician for hypertension, his blood pressure was 190/110. He weighed 190 pounds. Gynecomastia was still present. He complained of headaches, weakness, and left flank pain. The left-sided abdominal mass was still present. The level of blood urea nitrogen was 11.2 mg. per 100 ml. A chest roentgenogram showed left ventricular hypertrophy and no intrathoracic metastases.

On January 15, 1959, an intravenous pyelogram (Fig. 8) revealed a large mass in the upper left abdomen obscuring the outline of the left kidney, which was nonfunctional. On the right, the upper urinary tract and ureter were apparently normal.

FIG. 8. *Case 1.* Intravenous pyelogram, January 15, 1959, showing large mass in the upper left abdomen and no excretion of the contrast medium by the left kidney.

On March 12, 1959, the patient complained of pain in the back, palpitation, and weakness. His condition was otherwise unchanged.

He was not seen at the hospital again, but died at home on July 25, 1959.

Case 2

C. H., a 43-year-old white male, was in the hospital from April 25, 1950 to June 12, 1950 because of bilateral tender gynecomastia of three years' duration (Fig. 9). He denied changes in libido and other genitourinary symptoms. He had noted a gradual gain in weight over a five-year period.

FIG. 9. *Case 2.* Gynecomastia, showing hypertrophied breast tissue under the areola.

On physical examination his height was 5 feet 9¾ inches, weight 169 pounds, and blood pressure 120/70 mm. Hg. Hypertrophied nipples and palpable glandular breast tissue were present bilaterally. A previously unnoted hard nodule was found in the superior pole of the right testis, extending down its posterior aspect. The right testis appeared heavier than the left. Results of routine laboratory studies were normal. On May 1, a test with "Prolan A" yeilded negative findings. On April 26, a chest roentgenogram was unremarkable except for obliteration of the right costophrenic angle and large breast shadows. An intravenous pyelogram on May 2, 1950, showed nothing abnormal except for minimal redundancy of the right proximal ureter.

On May 5, 1950, a *right radical orchiectomy* was performed.

The gross pathology report was as follows: The right testis and attached 9.0 cm. of cord weighed 45.0 Gm. The tunica vaginalis was thin and moderately injected; the lower pole of the epididymis was firm and slightly thickened. On section of the testis, there was a sharply demarcated mass in the upper pole. It measured 3.0 ×2.0 cm., was soft, lobulated and yellowish-grey in color, and contained scattered small cystic areas with hemorrhages. There were no abnormalities of the vas deferens.

Microscopic examination: The neoplasm consisted of sheets of cells which were arranged in incomplete large lobules. Cellularity was moderate. The cells were medium sized and varied from polygonal to spindle-shaped in compressed areas (Fig. 10). Cell borders were poorly defined; the cytoplasm was eosinophilic and occasionally granular. The nuclei were round and uniform, containing prominent nucleoli and fine chromatin. The tumor cells were of monotonous uniformity. There were no mitotic figures.

The adjacent testicular parenchyma contained a microscopic satellite tumor which was similar to the main tumor mass. Maturation and spermatogenesis were active in the tubules.

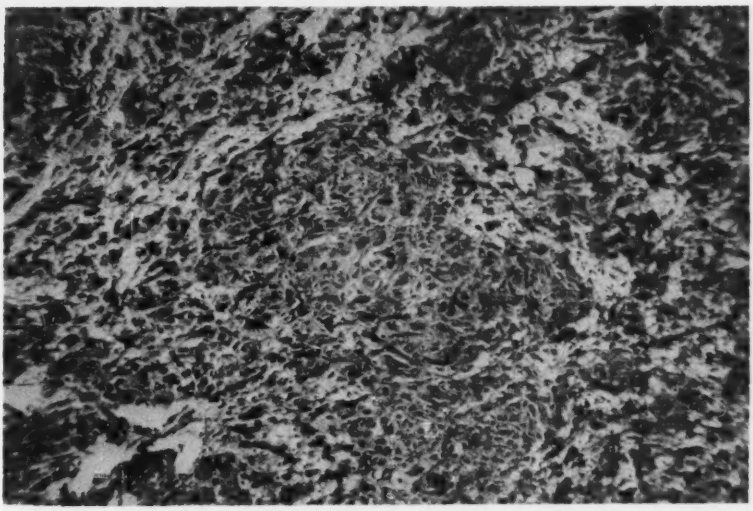

FIG. 10. *Case 2.* Organoid arrangement of uniform polygonal and spindle-shaped cells in the testicular tumor. (Hematoxylin and eosin, reduced from 125×.)

Follow-up examination on May 20, 1958, revealed the persistence of gynecomastia, a blood pressure of 136/88, and weight 157½ pounds. The leukocyte count, hemoglobin level, and results of urinalysis were within normal limits. A chest roentgenogram and intravenous pyelogram showed nothing abnormal.

The patient has been seen periodically and is living and well approximately ten years after orchiectomy.

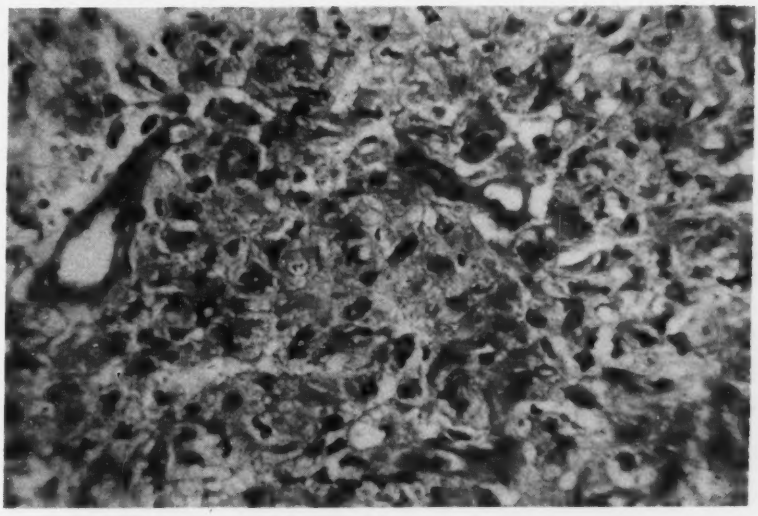

FIG. 11. *Case 2.* Testicular tumor. Uniform cellularity of cells, which vary from polygonal to spindle-shaped (Hematoxylin and eosin; 537×.)

TABLE 1. HORMONE EXCRETION AND PBI LEVEL—CASE 1

	Urine vol. (ml.)	Urinary excretion per 24 hours							Serum PBI (μg./100 ml.)
		17-OH-corticosteroids (mg.)	Gonadotropins (mouse units)	17-Ketosteroids (mg.)	Estrogens (μg.)				
					Total	Estrone	Estradiol	Estriol	
Normal standards		3–11	6–50	8–22	In males 4–25				4–8
Case 1									
May 22, 1956		11.1†	<6†	302†					6.3
Dec. 19, 1957	2450	12.27	<6.6	1156					
Feb. 27, 1958	1560	14.77	<6.6	1248					
Apr. 4, 1958	1800	12.11		1017	700‡	489‡	74‡	137‡	
July 14, 1958	1740	8.69							
Oct. 14, 1958	2900	5.1	<6.6	1473					
Jan. 15, 1959	1675		6.6§						
Mar. 12, 1959	2575	44.3		1860	480‡	325‡	55‡	100‡	

† Dr. J. H. U. Brown's Laboratory, Emory University.
‡ Bioscience Laboratories, Los Angeles, California.
§ Result positive in 1 mouse out of 3.

DISCUSSION

Since interstitial cells appear to be the source of testicular androgen (3), it is not surprising that interstitial-cell tumors produce sexual precocity when they occur in children (14). Gynecomastia occurring in the adult, as demonstrated by the 2 present cases, raises the question whether interstitial-cell tumors produce estrogens or whether the gynecomastia is an effect of androgens, since transitory gynecomastia is said to occur after administration of methyltestosterone (5).

The urinary estrogens in Case 1 (Table 1) were markedly increased, but so were the urinary 17-ketosteroids, which reached a level of 1860 mg. per twenty-four hours, and appeared to increase in correlation with the course of the disease. The elevated estrogen levels in Case 1 may explain the absence or undetectable levels of gonadotropins. The late rise in urinary 17-hydroxycorticoids in Case 1 is not readily explainable. The endocrine determinations in Case 2 (Table 2) were generally within normal limits.

Gynecomastia has been observed in dogs (6, 7) with interstitial-cell

TABLE 2. HORMONE EXCRETION—CASE 2

	Urine vol. (ml.)	Urinary excretion per 24 hours		
		17-OH-corticosteroids (mg.)	Gonadotropins (mouse units)	17-Ketosteroids (mg.)
Normal standards		3–11	6–50	8–22
Case 2				
May 1, 1950			"Negative"*	
Nov. 13, 1957	1200			10.08
May 20, 1959	850	7.0	>6.6<52.8	6.12

* VA Hospital, Hines, Illinois.

tumors. Increased urinary estrogen and increased amounts of estrogen in the tumor itself have also been demonstrated in a dog (7).

It is quite evident that germinal-cell tumors of the testis may also produce gynecomastia (8), so that the combination of testicular tumor and gynecomastia is not specifically diagnostic of an interstitial-cell tumor. Increased urinary estrogen excretion has been observed in patients with interstitial-cell tumors (9–11). Elevation of urinary 17-ketosteroids (12), occasionally to extremely high levels (13) comparable to those in Case 1, has also been observed. Although a high level of urinary gonadotropins has been reported (14), in our Case 1 gonadotropin excretion was extremely low, and it was normal postoperatively in Case 2.

It is of interest that interstitial-cell tumors have been produced in animals by the administration of estrogens and estrogenic substances (15–18). However, tumors have also been produced by transplanting part of the testis to the spleen (19).

Occasionally interstitial-cell tumors are associated with a hydrocele (20, 21). Patient J. L. (Case 1) was initially believed to have a hydrocele before a testicular tumor was suspected. A paratesticular location (22) of an interstitial-cell tumor has also been described. These possibilities emphasize the need for careful examination of the scrotal contents in cases of gynecomastia.

Although interstitial-cell tumors are generally benign, as demonstrated by Case 2, they can metastasize, as demonstrated by Case 1. Perhaps the most unusual aspect of the metastasis is its relatively slow growth. In Case 1 the intra-abdominal metastasis was discovered two years after removal of the primary tumor, but death did not ensue until three years later and at that time there was no x-ray evidence of pulmonary metastasis. This would suggest that operative removal of an interstitial-cell tumor metastasis may be justified. The location of the metastasis in Case 1 prevented operative removal. Later the metastatic growth destroyed the function of the left kidney, and this may have been related to the onset of hypertension.

Acknowledgment

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Letter to the Editor

ESTRIOL IN BLOOD

To the Editor

May we call your attention to a recent paper—Touchstone J. C. and Greene, J. W.: "Free estriol in blood plasma" (1)—published in the April issue of your periodical?

In this paper the authors state that among other investigators "Diczfalusy and Lindkvist (2) . . . have described chemical methods for the estimation of estrone, estradiol-17β and estriol in blood and plasma." They also state that "In these reports (excepting that of Slaunwhite and Sandberg who used hydrolysis) definite criteria were not presented for the identity of the final fraction assayed as estrone, estradiol-17β, or estriol."

We consider these statements erroneous. The quoted paper by Diczfalusy and Lindkvist (2) does not deal at all with blood or plasma estrogens, but with the isolation and estimation of "free" estrogens in human placentae. Touchstone and Greene apparently wanted to make reference to another paper published by us, entitled "Tissue concentration of oestrone, oestradiol-17β and oestriol in the human foetus" (3). This paper deals with estrogen assays in umbilical cord blood, and with the isolation and identification of estriol in extracts of cord blood. Our conclusion that the material isolated from cord blood was identical with estriol was based (in addition to estimation of the partition coefficients of estriol-3-methyl-ether and of estriol-3-methyl-ether-16, 17-diacetate in Craig liquid-liquid discontinuous countercurrent distributions) on complete agreement of the infrared spectrum of the methylated estriol fraction with that of an authentic estriol-3-methyl-ether reference compound.

The plasma estriol value of 7.8 μg. per 100 ml., mentioned in the paper of Touchstone and Greene (1), falls within the 95 per cent fiducial limits of the normal concentration (3.9–8.5 μg. per 100 ml. of cord blood) we established in 9 assays on 41 samples of cord blood. As it appears from the data presented in our paper (3), recovery experiments carried out with estrone, estradiol-17β, estriol and sodium estriol glucosiduronate added to cord blood indicated satisfactory accuracy of the method employed.

Egon Diczfalusy, M.D.
Anne-Marie Magnusson (Fil. Kand)

Hormone Laboratory,
Department of Women's Diseases,
Karolinska sjukhuset,
Stockholm 60, Sweden,
May 14, 1960

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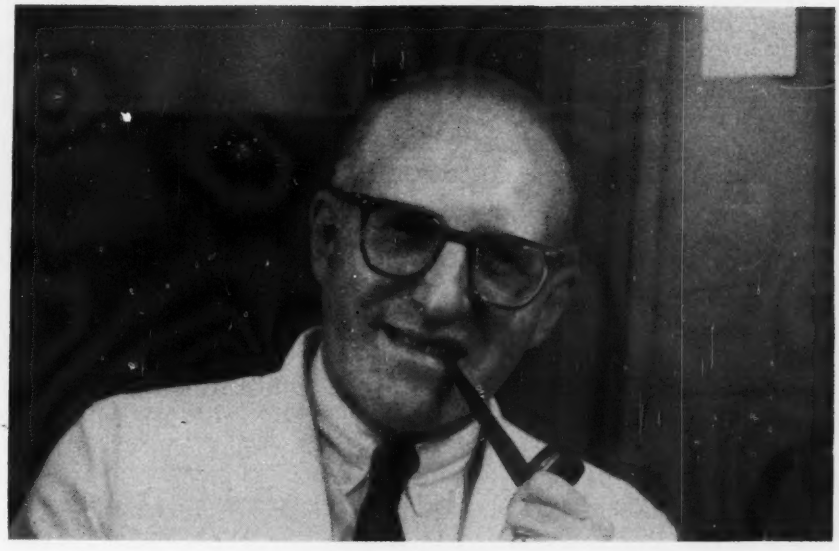

JOSEPH W. JAILER

IN MEMORIAM
JOSEPH WILLIAM JAILER, MD., Ph.D
1914-1960

THE sudden death of Dr. Joseph W. Jailer on August 23, 1960 is a heavy loss to Columbia, to the medical community of New York City, and to students of hormonal disease all over the world. It is fitting that we should pay honor to the memory of this remarkable man, who died, ironically, just at the time when he had achieved most of his major goals, and when his national and international reputation in endocrinology had become secure.

Joseph Jailer was physically and spiritually a product of New York City. Born here on July 7, 1914, he received his early education in New York's public schools and graduated with honors from the College of the City of New York in 1934. After winning the degree of Master of Science at New York University in 1936, he went to the Department of Anatomy at the College of Physicians and Surgeons, Columbia University. There, he stud-

ied under Professor Philip E. Smith, whom he came to regard as his scientific father. His meticulous studies of the metabolic changes that follow hyper- and hypofunction of the testes and thyroid in primates earned him the Doctorate of Philosophy in 1940.

Determined to continue a life of basic research in endocrinology, he was persuaded to study medicine by his colleagues and teachers, who wished to make his considerable talents available to the study of endocrine problems in man. It was principally the late Professor Earl T. Engle who kept him at his medical studies when he would have preferred to be working in the laboratory. He graduated from the College of Physicians and Surgeons in 1943, a member of Alpha Omega Alpha, and served his internship in medicine at the Presbyterian Hospital, New York.

During World War II, Dr. Jailer served in the Army Medical Corps, becoming Chief of the Division of Chemistry of the Army Medical School in Washington. While in the service, he carried on important work in the pharmacology of barbiturates and antimalarial drugs. He returned to civilian life in 1946, and held fellowships from the Rockefeller and Damon Runyon Foundations, joining the Faculty of Medicine at Columbia in 1947. Thereafter, he rose rapidly through the Faculty ranks to become Associate Professor of Clinical Medicine (assigned to Obstetrics and Gynecology) and Associate Attending Physician, Presbyterian Hospital, in 1954.

The extraordinary feature of Dr. Jailer's work was its wide range. Between 1934 and 1960, he wrote more than 85 scientific articles and chapters in technical works dealing with genetics, immunology, microscopic anatomy, the chemical measurement of drugs and hormones in body fluids, and the metabolism of estrogens. He reported studies of nearly every endocrine organ: the pituitary, the adrenal medulla, the ovary, the testis, the placenta and the pancreatic islets. In 1949, he became particularly interested in the adrenal cortex, and his contributions to the understanding of the physiology of this gland placed him in the first rank of investigators. Alone, and with several collaborators, he reported investigations of the adrenal cortex in pregnancy and in gynecologic disorders. He made major advances in the study of Cushing's syndrome and threw much light on the nature of its cause. Perhaps his most important single contribution was the brilliant insight that elucidated the enzymatic basis of congenital adrenal hyperplasia.

As a teacher, Dr. Jailer had wide influence, both in the instruction of medical students and in the specialized clinical and laboratory training of graduate physicians. More than 20 post-doctoral Fellows came under his guidance. They continue to spread his teachings in this country, the United Kingdom, Italy, France, and even behind the Iron Curtain. His methods

of instruction were gentle, and inspired respect and affection rather than awe.

At the time of his death, he was carrying a work load that attested to his great versatility. He was Director of the Endocrine Diagnostic Laboratory, held several research grants that required detailed administrative work, made ward rounds in general medicine as well as his special field, and carried on an active practice. Outside the institution, he lectured often, and was especially interested in communicating the fruits of his studies to the staffs of small hospitals nearby. In addition, he was a member of many learned societies: the Harvey Society, the New York Diabetic Association, the New York Academy of Sciences, the American Physiological Society, the American Association of Anatomists, the American Society for Clinical Investigation, and the Association of American Physicians. He served as a member of the editorial board of two journals: the Proceedings of the Society for Experimental Biology and Medicine and The Journal of Clinical Endocrinology and Metabolism. He was consultant to the Veterans Administration and the National Science Foundation, and was Chairman of the Study Section on Cancer Chemotherapy of the United States Public Health Service.

Joe Jailer was what Samuel Johnson would have called a "clubbable man," a man you could love. Gay and witty, he had his gloomy moments as we all do, but in all the years he was at Columbia he was never once seen to be seriously angry. His telephone rang incessantly, but he always answered with good cheer. Whether he was talking to a Washington dignitary or to a patient with some insoluble medical problem, his manner was always the same—a happy blend of courtesy and whatever indefinable qualities go to make up the man we would all like to be and seldom are—the gentleman, the healer and the comforter.

He was a good companion, a wise teacher and physician, and a scientist of real depth. His patients, students and colleagues will not forget his unfailing gentleness, his humor, his enormous fund of knowledge, and—his most priceless characteristic—the richness of his imagination. Their sorrow at his early death will be only slightly tempered by gratitude for having been exposed to the grace of his personality and the sparkle of his mind.

NICHOLAS P. CHRISTY, M.D.

The Endocrine Society

The 1961 Annual Meeting

The Forty-Third Annual Meeting of the Endocrine Society will be held in the Hotel Biltmore, New York, N. Y., Thursday, Friday and Saturday, *June 22, 23 and 24, 1961.*

The Scientific Sessions will be held from 9:00 a.m. to 5:00 p.m. daily and in addition there will be simultaneous afternoon sessions. The annual dinner is scheduled for Friday, June 23, at 7:30 p.m., preceded by cocktails at 6:30 p.m.

All members are urged to make their hotel reservations immediately. The Biltmore will hold 300 bedrooms for members until May 1, 1961, after which time the hotel will not guarantee further reservations. Therefore it is imperative that you make your reservations early, directly with the hotel, advising them of time and date of arrival and departure. If you plan on remaining through June 26 for the American Medical Association and other meetings, it is imperative that your reservations be made from June 26 on, directly through the A. M. A. Housing Bureau. Make your reservations early and avoid disappointment. Hotel reservation card will be mailed to members shortly after January 1, 1961.

Final program, membership card and advance registration forms will be sent on May 1, 1961 to members whose current dues have been paid.

Those wishing to present papers, which will be strictly limited to ten minutes, should send an original and four copies of the title and abstract to the Vice-President, Dr. Roy Hertz, National Cancer Institute, Bethesda, Maryland, not later than *February 15, 1961.* It is imperative that the abstracts be informative and complete with results and conclusions—not a statement that those will be presented at the meeting—in order that they may be of reference value and suitable for printing in the program. The reading and processing of approximately 200 abstracts submitted each year and compiling of the program from these involves a tremendous amount of time and effort on the part of the Program Committee.

THE COUNCIL REQUESTS THAT AUTHORS ADHERE STRICTLY TO THE FOLLOWING RULES WHEN SUBMITTING ABSTRACTS; OTHERWISE THEY CANNOT BE CONSIDERED:

1. IT IS ASSUMED THAT ABSTRACTS SUBMITTED FOR THIS PROGRAM HAVE NOT AND WILL NOT BE SUBMITTED ELSEWHERE.
2. Abstracts may not exceed 200 words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulae cannot be used.
3. The title heading must be arranged as follows:
   Line 1. Title, not to exceed 15 words;
   Line 2. Author/s. The name of each nonmember-author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of nonmembers who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be written after his name.
   Line 3. Institution of origin and city in which institution is located.
4. Authors who wish receipt of their abstracts acknowledged should enclose self-addressed post card with the title of the abstract noted thereon.
5. Authors are also to enclose 3×5 inch filing cards, one for each author, giving his name and initials in the upper right-hand corner, and the complete title of the abstract with all the authors listed in the center of the card. There should be a second card enclosed listing the title and all authors, and the mailing address of the senior author. This is necessary for indexing. Senior authors will be notified of the acceptance of their papers for the final program.
6. The body of the abstract, typed double space, should follow the heading. The original copy should be on bond paper. The original and four copies should be forwarded to Dr. Hertz.
7. Abstracts should be letter perfect, since there will be no opportunity for proof reading by the authors.

The 1961 Awards

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors. Endocrine Society awards are limited to citizens of the United States and Canada.

FRED CONRAD KOCH AWARD

In 1957 a substantial legacy was bequeathed to the Society by the late

Elizabeth Koch for the purpose of establishing the Fred Conrad Koch Memorial Fund in memory of her late husband, Distinguished Service Professor of Physiological Chemistry at the University of Chicago and pioneer in the isolation of the androgens. This is the highest honor of The Endocrine Society and is represented by a medal known as the Koch Medal of The Endocrine Society. The medal, as well as an honorarium of $3,500, is to be given annually to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada.

This Award was first presented in 1959, to Dr. W. W. Swingle and in 1960 was presented to Dr. Emil Witschi. The Koch Medal has replaced the Medal of The Endocrine Society which was established in 1954.

The Ciba Award

The Ciba Award is given in recognition of the meritorious accomplishments of an investigator in the field of basic or clinical endocrinology who has not reached his thirty-sixth birthday before June 1 of the year in which the Award is presented. This Award was established in 1942 and first presented in 1944. The Award is presently in the amount of $2,500.

The Ayerst and the Squibb Fellowships

The Ayerst Fellowship was established in 1947 and the Squibb Fellowship in 1956. They are designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. Each Fellowship is awarded on alternate years and the stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

The Upjohn Scholar of the Endocrine Society

The Council of The Endocrine Society has established a category of Scholars. A grant has been made available through the generosity of the Upjohn Company, and will be awarded to an established investigator or teacher in the field of endocrinology who wishes to extend the opportunities for work either in this country or abroad.

The award will not exceed $2,500 annually and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Fred Conrad Koch Award, the Ciba Award, and the Ayerst and the Squibb Fellowships may be made by any member of The Endocrine Society. They should be submitted on forms which may be obtained from the Office of the Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma. Completed nominations should be returned to the Secretary not later than *October 15* each year.

Proposals for appointments as a Scholar of The Endocrine Society should be made in writing by the individual, and addressed to the Secretary of the Society. They should be submitted by *October 15* each year.

The American Goiter Association

The 1961 Annual Meeting

The next Annual Meeting of the American Goiter Association will be held in the Warwick Hotel, Philadelphia, Pennsylvania, *May 3–6, 1961.* Arrangements are being made for a Clinical Day in the Philadelphia Hospitals on May 3. Scientific papers will be presented in the Warwick Hotel on May 4, 5 and 6. For further information address the Secretary, John C. McClintock, M.D., 702 Madison Avenue, Albany 8, N.Y.

The Van Meter Prize Award for 1961

The American Goiter Association, Inc. again offers the Van Meter Prize Award of $300.00 to the essayist submitting the best manuscript of original and unpublished work concerning "Goiter—especially its basic cause." The studies so submitted may relate to any aspect of the thyroid gland in all of its functions in health and disease. The Award will be made at the Annual Meeting of the Association in the Warwick Hotel, Philadelphia, Pennsylvania, May 3–6, 1961. A place on the program will be reserved for the winning essayist if he can attend the meeting. When more than one author's name appears on the manuscript the authors will be asked to designate a single recipient to receive the award.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary; John C. McClintock, M.D., 702 Madison Avenue, Albany 8, N. Y., *not later than January 1, 1961.* Manuscripts that do not conform to these requirements will not receive consideration. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

Book Register

Congenital Malformations. Ciba Foundation Symposium edited by G. E. W. WOLSTENHOLME, O.B.E., M.B., and C. M. O'CONNOR, B.Sc. Twenty-nine investigators in differing fields of research took part in this Sympsoium, which covered the following subjects: Malformations in a population observed for five years after birth, genetical causes of malformation, chromosomal abnormalities, environmental factors, teratogenic effects of tumor-inhibiting chemicals in the fetal rat, the teratogenic action of antibiotic actinomycin D, teratogenic effects of pteroylglutamic acid deficiency, the modification of agents exerting a deleterious effect on the mammalian embryo, congenital runts, causes of anencephaly, role of prediabetes and hypothyroidism in congenital malformations, and the association of hydramnios with congenital malformations; 308 pages; 91 illustrations; 1960. Little, Brown and Company, Boston, Mass. Price $9.00.

Diverticulitis. By SARA M. JORDAN, M.D., Founder and Former Head of the Department of Gastroenterology, The Lahey Clinic, Boston, Massachusetts, and RUSSELL S. BOLES, JR., M.D., Member of the Staff, Department of Gastroenterology, The Lahey Clinic. A Modern Medical Monograph, edited by IRVING S. WRIGHT, M.D., and RICHARD H. ORR, M.D. Contents: 1) Nomenclature; 2) Historical review (1904–1959); 3) Diverticulosis—pathogenesis, true and false diverticula, incidence, diagnosis; 4) Diverticulitis—pathogenesis, incidence, diagnosis, complications, and medical treatment; 90 pages; 15 figures; 1960. Grune & Stratton, Inc., New York, N. Y. Price $4.75.

Human Pituitary Hormones. Volume XIII. Ciba Foundation Colloquia on Endocrinology. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.B., and C. M. O'CONNOR, B.Sc. In honor of PROF. B. A. HOUSSAY. Thirty-two international authorities took part in this Symposium in Buenos Aires, Argentina. The subjects covered were: Radiologic anatomy of the human pituitary; systemic fractionation of human pituitaries; human pituitary growth and gonadotropic hormones; immunologic studies of human growth hormone; growth hormone in relation to mobilization of fatty acids, metabolic action, urinary calcium excretion, variability in physiologic response and aldosterone secretion; human pituitary FSH; gonadotropin and ICSH assays in urine; ACTH and melanocyte-stimulating hormone from human pituitary glands; and the blood concentration of TSH in normal subjects and in thyroid disease; 336 pages; 86 illustrations; 1960. Little, Brown and Company, Boston, Mass. Price $9.50.

Insulin. British Medical Bulletin, Volume 16, No. 3. This colloquium, edited by PROF. F. G. YOUNG, contains sixteen papers by authorities in the field. The articles include the history of insulin over a period of forty years (by C. H. Best), the chemistry of insulin (F. Sanger) and the chemistry and metabolism of polypeptide hormones, methods of insulin assay, insulin in blood, insulin antagonists and antibodies, fatty-acid, insulin and protein metabolism, the mechanism of action of insulin and relation to endocrine disorders, insulin in clinical practice, and the synthetic hypoglycemia-producing substances and their clinical effectiveness. British Medical Bulletin, 65 Davies Street, London, W.1, England. Price $3.25.

Die Oedeme. Physiopathologie und Therapie der Salz- und Wasserretention. By PD. DR. JEAN FABRE, Geneva, in association with DR. ANDREAS FANCONI and DR. MARTIN ROTHLIN. Foreword by PROF. DR. RENÉ S. MACH, Geneva. (In German.) The clinical and experimental advances in the knowledge of edema during the past twenty years are presented in an easily understandable manner, including gynecologic, pediatric and endocrinologic aspects. Part 1 deals with the physiology of water and electrolyte metabolism, the antidiuretic hormone, aldosterone, and the regulation of intravascular fluid volume. Part 2 deals with the pathologic physiology of edema, differentiating the various kinds, *e.g.*, cardiac, renal, hepatic, allergic, adrenocortical hormone-induced, pregnancy-related, and deficiency-related. Part 3 deals with the management of edema, including diets, diuretics, fluid intake and adrenocortical hormone therapy; 304 pages; 42 figures; 19 tables; 960 references; 1960. Benno Schwabe & Co., Basel, Switzerland. In the U.S.A., Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16, N. Y. Price $9.50.

The Population Council, Annual Report 1959. The Executive Officers report on the Demographic Program, the Program of Medical Research and the publications resulting from Population Council Grants. Mr. John D. Rockefeller 3rd's speech on "A Citizen's Perspective on Population" is appended; 52 pages; 1960. Administrative Office of the Population Council, 230 Park Avenue, New York 17, N. Y.

Public Health Service Publications. U. S. Department of Health, Education, and Welfare, National Institutes of Health, Bethesda 14, Maryland. Obtainable from U. S. Public Health Service, Washington 25, D. C.

No. 702. Public Health Monograph No. 63. Academy of Medical Sciences of the USSR. History and Organization, 1944–1959. By GALINA V. ZARECHNAK, Ph.D. Prepared in the National Library of Medicine for the Russian Scientific Translation Program, Public Health Service. The monograph outlines the background of medical research in the USSR, organization and staff, Academy personnel and activities, research planning, trends in medical research and objectives of the seven-year plan, 1959–1965; 48 pages; paper; 1960.

No. 745. Highlights of Research Progress in Allergy and Infectious Diseases, 1959. Prepared by the National Institute of Allergy and Infectious Diseases as background material for submission at congressional hearings on appropriations for fiscal year 1962. There are sections on Virus Diseases, Allergy-Immunology, Bacterial Diseases, Cell Biology, Parasitic Diseases, Fungus Diseases and Rickettsial Diseases; 53 pages; paper; 1960. Supt. of Documents, U. S. Government Printing Office, Washington 25, D. C. Price 25 cents.

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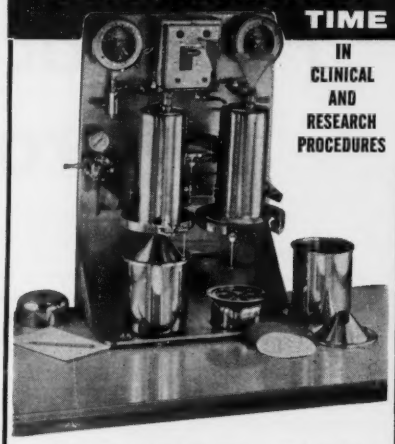

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